

Canadian Journal of Diabetes

Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada

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TABLE OF CONTENTS

Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada

Notes to Readers	iv
2008 Clinical Practice Guidelines Committees	v
Acknowledgements	x
Introduction	S1
Methods	S5
Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories	S10
Screening for Type 1 and Type 2 Diabetes	S14
Prevention of Diabetes	S17
Management	
<i>Organization of Diabetes Care</i>	S20
<i>Self-management Education</i>	S25
<i>Targets for Glycemic Control</i>	S29
<i>Monitoring Glycemic Control</i>	S32
<i>Physical Activity and Diabetes</i>	S37
<i>Nutrition Therapy</i>	S40
<i>Insulin Therapy in Type 1 Diabetes</i>	S46
<i>Pharmacologic Management of Type 2 Diabetes</i>	S53
<i>Hypoglycemia</i>	S62
<i>Hyperglycemic Emergencies in Adults</i>	S65
<i>In-hospital Management of Diabetes</i>	S71
<i>Management of Obesity in Diabetes</i>	S77
<i>Psychological Aspects of Diabetes</i>	S82
<i>Influenza and Pneumococcal Immunization</i>	S86
<i>Pancreas and Islet Transplantation</i>	S88
<i>Complementary and Alternative Medicine in the Management of Diabetes</i>	S91
Macrovascular and Microvascular Complications	
<i>Identification of Individuals at High Risk of Coronary Events</i>	S95
<i>Screening for the Presence of Coronary Artery Disease</i>	S99
<i>Vascular Protection in People With Diabetes</i>	S102
<i>Dyslipidemia</i>	S107
<i>Treatment of Hypertension</i>	S115
<i>Management of Acute Coronary Syndromes</i>	S119

<i>Treatment of Diabetes in People With Heart Failure</i>	S123
<i>Chronic Kidney Disease in Diabetes</i>	S126
<i>Retinopathy</i>	S134
<i>Neuropathy</i>	S140
<i>Foot Care</i>	S143
<i>Erectile Dysfunction</i>	S147

Diabetes in Children

<i>Type 1 Diabetes in Children and Adolescents</i>	S150
<i>Type 2 Diabetes in Children and Adolescents</i>	S162

Diabetes in Special Populations

<i>Diabetes and Pregnancy</i>	S168
<i>Diabetes in the Elderly</i>	S181
<i>Type 2 Diabetes in Aboriginal Peoples</i>	S187
<i>Type 2 Diabetes in High-risk Ethnic Populations</i>	S191

Appendices

<i>Appendix 1. Etiologic Classification of Diabetes Mellitus</i>	S194
<i>Appendix 2. Sample Diabetes Patient Care Flow Sheet for Adults</i>	S195
<i>Appendix 3. Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes</i>	S197
<i>Appendix 4. Rapid Screening for Diabetic Neuropathy</i>	S199
<i>Appendix 5. Diabetes and Foot Care: A Patient's Checklist</i>	S200
<i>Appendix 6. Diabetic Foot Ulcers: Essentials of Management</i>	S201

NOTES TO READERS

Overview

The Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada are intended to guide practice and are not intended to serve as a comprehensive text of diabetes management, nor are they intended to set criteria for research protocols. These guidelines are intended to inform general patterns of care. These guidelines are also intended to enhance diabetes prevention efforts in Canada and to reduce the burden of diabetes complications in people living with this disease.

As per the Canadian Medical Association *Handbook on Clinical Practice Guidelines* (Davis D, et al. Ottawa, ON: Canadian Medical Association; 2007), guidelines should not be used as a legal resource in malpractice cases as “their more general nature renders them insensitive to the particular circumstances of the individual cases.” Healthcare professionals must consider the needs, values and preferences of individual patients, use clinical judgement, and work with available human and healthcare service resources in their settings. These guidelines were developed using the best available evidence. It is incumbent upon healthcare professionals to stay current in this rapidly changing field.

Unless otherwise specified, these guidelines pertain to the care of adults with diabetes. Two chapters – “Type 1 Diabetes in Children and Adolescents” and “Type 2 Diabetes in Children and Adolescents” – are included to highlight aspects of care that must be tailored to the pediatric population.

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Introduction

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Vincent Woo MD FRCPC

Since the publication of the 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada, the Clinical & Scientific Section of the Canadian Diabetes Association has published comprehensive, evidence-based recommendations for healthcare professionals to consider in the management of their patients living with diabetes. In the 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, the evidence from the 1998 recommendations was completely reviewed, and recommendations on the prevention of type 2 diabetes were enhanced. In developing the 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, volunteers from the Clinical Practice Guidelines Expert Committee assessed the peer-reviewed evidence published since 2003 relevant to the prevention and management of diabetes, and then incorporated the evidence into revised diagnostic, prognostic and therapeutic recommendations for the care of Canadians living with diabetes, as well as recommendations for preventive measures for populations at high risk of developing type 2 diabetes.

A number of important changes have occurred in the development of the 2008 clinical practice guidelines. The Expert Committee has been expanded to include 76 volunteers, representing a broader variety of healthcare professionals from across Canada. Expert Committee members bring expertise from diverse practice settings, including multiple specialists, family physicians, nurses, dietitians, pharmacists and other healthcare professionals.

In addition to updating previous chapters, a number of new chapters have been added to the 2008 guidelines, widening their scope to other areas of diabetes care and complications. It is hoped that primary care physicians and other healthcare professionals who care for people with diabetes or those at risk of type 2 diabetes will continue to find the evidence compiled in these guidelines a vital aid and resource in their efforts. It is our hope that, ultimately, these guidelines will lead to improved quality of care, reduced morbidity and mortality from diabetes and its complications, and a better quality of life for people living with this chronic disease.

UPDATES

In the past, full updates of these guidelines have occurred every 5 years. However, chapter updates and position statements are produced on an “as needed” basis. These updates are posted on the Canadian Diabetes Association

website at <http://www.diabetes.ca> and published in the *Canadian Journal of Diabetes*.

PATIENT ISSUES

People with diabetes are a diverse and heterogeneous group, and it must therefore be emphasized that treatment decisions must be individualized. Guidelines are meant to aid in decision making, but the therapeutic decisions are made at the level of the patient-physician relationship. Evidence-based guidelines try to weigh the benefit and harm of various treatments; however, patient preferences are not always included in clinical research, although quality-of-life assessments are becoming standard practice. It is important to remind healthcare professionals about the need to incorporate patient values and preferences into decision making (1).

THE CHALLENGE OF DIABETES

Diabetes is a serious condition with potentially devastating complications that affects all age groups worldwide. In 1985, an estimated 30 million people around the world were diagnosed with diabetes; in 2000, that figure rose to over 150 million, and it is projected to rise further to 380 million by 2025 (2). The International Diabetes Federation states that “every ten seconds, two people are diagnosed with diabetes somewhere in this world,” and given the current trend, more people will have diabetes in 2025 than the current populations of the United States, Canada and Australia combined (3).

The impact of diabetes is felt in both developed and developing countries. For this reason, the 61st session of the United Nations General Assembly passed a resolution in 2007 recognizing November 14th as World Diabetes Day, and it encouraged all member states to develop national strategies and policies for the prevention, treatment and care of people with diabetes.

The impact of diabetes is also felt in Canada, where 1.8 million adult Canadians – 5.5% of the population – had diagnosed diabetes in 2005 (4). That is an increase from 1998, when the physician-diagnosed prevalence of diabetes in Canada was 4.8% (1 054 000 adult Canadians). Diagnosed diabetes has grown 70% since the publication of the 1998 Canadian Diabetes Association clinical practice guidelines. This number will continue to grow given Canada’s demographic trends. An aging population, increasing immigration from high-risk populations and growth in the Aboriginal

population will increase the burden of diabetes over the next 10 years. Researchers project an increase of diagnosed diabetes in Canada to 2.4 million by the year 2016 (5).

The rate of diagnosed diabetes contributes significantly to comorbidity and diabetes complication rates. Diabetes is the leading cause of blindness, end-stage renal failure and non-traumatic amputation in Canadian adults. Cardiovascular disease, the leading cause of death in individuals with diabetes, occurs 2- to 4-fold more often compared to people without diabetes. Approximately one-quarter of Canadians living with diabetes are also diagnosed with depression, and the combination of diabetes and depression is associated with poor compliance with treatment and increased healthcare costs (6,7). Eleven percent of Canadians living with diabetes also have 3 or more chronic health conditions, and compared to the general population, they are 4 times more likely to be admitted to a hospital or a nursing home, 7 times more likely to need home care and 3 to 5 times more likely to see a healthcare provider (8).

Diabetes and its complications increase costs and service pressures on Canada's publicly funded healthcare system. Because of poor compliance to evidence-based recommended management regimens, diabetes and its complications significantly contribute to the cost of primary healthcare, and add to waiting times for treatment in emergency departments and surgeries. Research indicates that 280 330 admissions into Canadian acute care hospitals in 2006 – or 10% of all such admissions – were related to diabetes or its complications (9,10).

Caution is required when identifying direct, indirect and induced costs for treating diabetes, given the differing estimates by different researchers (11-15). Nonetheless, in 2005, federal, provincial and territorial governments spent an estimated \$5.6 billion to treat people with diabetes and its complications within the acute healthcare system (5). This amount, equal to 10% of the annual cost of Canada's healthcare system, includes the cost of hospitalization for surgical and emergency care, in-hospital medications, devices and supplies, as well as physician and specialist visits. It does not include the costs of rehabilitation after major surgery or amputation, or the personal costs to the individual and family (e.g. a parent's inability to pay for a child's higher education).

Moreover, the trend of increased hospitalization has gone unchecked in the last 5 years. In Ontario, for example, research shows that little has changed in the rate of complications due to diabetes. Data analysis shows that approximately 4% of newly diagnosed diabetes patients end up in an emergency department or hospital for acute complications of their condition (16). The lack of change in the rate of complications suggests that despite the increasing evidence about the importance of managing diabetes effectively, little progress has been made in ensuring that people living with diabetes get the recommended care, education and management required to lower their risk of developing complications.

PREVENTION OF TYPE 2 DIABETES

Prevention of type 1 diabetes has not yet been successful; however, the evidence indicates that preventing or delaying the onset of type 2 diabetes results in significant health benefits, including lower rates of cardiovascular disease and renal failure; ~30 to 60% of type 2 diabetes may be prevented through early lifestyle or medication intervention (3).

The modifiable risk factors for type 2 diabetes are well known. By 2011, more than 50% of Canadians will be over 40 years of age and at risk for type 2 diabetes. Our lifestyles today contribute to unhealthy eating and physical inactivity. In 2005, 2 of 3 Canadian adults and nearly 1 of 3 children aged 12 to 17 years were overweight or obese (17), and are therefore at high risk of developing type 2 diabetes.

The Diabetes Prevention Program found that people at risk of developing type 2 diabetes were able to cut their risk by 58% with moderate physical activity (30 minutes a day) and weight loss (5 to 7% of body weight, or about 15 lb). For people over age 60, the risk was cut by almost 71% (18).

There remains an urgent and increasing need for governments to invest in research to define effective strategies and programs to prevent and treat obesity and to encourage physical activity. Health promotion and disease prevention strategies should be tailored to specific populations, and should include policies aimed at addressing poverty and other systemic barriers to health.

ADVOCACY AND OPTIMAL CARE

Effective diabetes care is supported by evidence-based clinical practice guidelines; regular monitoring of blood glucose, blood pressure and cholesterol levels; and ongoing feedback among all members of the diabetes health team to lower the risk and potential impact of serious complications for individuals with diabetes. Government investments in chronic disease management approaches offer an interdisciplinary approach recommended for effective diabetes care. A team of healthcare professionals – including physicians, nurses, diabetes educators, pharmacists and other healthcare experts who work together with the individual living with diabetes – is the recommended approach to achieve optimal care.

One of the key challenges of the chronic disease management approach for individuals living with diabetes is the greater level of self-management required in order for this approach to be effective. People with diabetes are asked to have the skills and abilities to reduce the physical and emotional impact of their disease, with or without the collaboration of their healthcare team. There is no question that self-management skills complement the expertise and care provided by members of the diabetes health team; however, the chronic disease management model is a paradigm shift from the traditional primary or acute care model. People with diabetes require training in goal setting, problem solving and planning skills, all of which are critical components of self-management. They also need access to a broad range

of tools, including medications, devices and supplies to help them achieve the recommended blood glucose, cholesterol and blood pressure targets. Health outcomes depend on managing the disease effectively, and without access to the necessary tools and strategies, Canadians living with diabetes will not be able to achieve optimal results.

All levels of government should commit to a strategy that ensures that the personal cost of managing diabetes and its complications will not be a barrier to the effective management of this chronic disease. More than ever, Canada needs to shift to an evidence-based model of managing diabetes. With healthcare sustainability remaining at the top of the Canadian political agenda, all levels of government require justification for healthcare expenditures, and evidence-based guidelines can be used to make funding decisions that improve cost and efficiency in healthcare delivery.

RESEARCH

Canada continues to be a world leader in diabetes research. This research is essential for continued improvement in the lives of people with diabetes. Regulatory agencies should not apply these guidelines in a rigid way with regards to clinical research in diabetes. There are already many safeguards in place to protect clinical trial subjects, including ethics review boards and the integrity of Canadian researchers. It is suggested that study protocols can include guideline recommendations, but individual decisions belong in the domain of the patient-physician relationship. The merits of each research study must be assessed individually so as not to block or restrict the pursuit of new information. The Canadian Diabetes Association welcomes the opportunity to work with regulatory agencies to enhance research in Canada and ultimately improve the care of people with diabetes.

DISSEMINATION AND IMPLEMENTATION

The challenges of effective dissemination and implementation of the 2 previous clinical practice guidelines were assessed prior to the launch of the 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. In response, strategies were developed to increase practitioner implementation and to improve patient care and health outcomes. The Expert Committee established a Dissemination & Implementation Committee with the mandate to develop a strategic plan to be implemented at the launch of the guidelines. More than 80 volunteers from across Canada were involved in creating a 3-year plan to translate the evidence compiled in the guidelines into community practice. The guidelines will continue to be available on the web, and summary articles will be placed in journals and newsletters. In addition, key messages and tools supporting specific themes from the guidelines will be highlighted in focused awareness campaigns over the next 3 years. Primary care physicians, healthcare providers, government officials, Canadians living with

diabetes and the general public continue to be the audiences for these campaigns.

CONCLUSION

Diabetes is a complex and complicated disease. The burgeoning evidence on new technologies and therapeutic treatments is rapidly expanding our knowledge and ability to manage diabetes and its complications; at the same time, however, it is challenging physicians and other healthcare professionals who care for people with diabetes.

These 2008 clinical practice guidelines are evidence-based recommendations that provide a useful reference tool to help healthcare professionals translate the best available evidence into practice. A cost-benefit analysis of the 2008 recommendations is not included. The most effective therapies may not be the most cost-effective ones. The hope is that these guidelines will provide government officials with the evidence they need when rationalizing access to healthcare so that the potentially beneficial health outcomes are maximized for people living with diabetes. Moreover, the issue of evidence-based versus cost-effective healthcare is an ethical debate that should involve all citizens, because the outcome of this debate ultimately impacts every Canadian.

Physicians, other healthcare professionals and general readers are encouraged to judge independently the value of the diagnostic, prognostic and therapeutic recommendations published in the 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. By doing so, they will remain current in this ever-changing field.

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Methods

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Gillian Booth MD MSc FRCPC, Sarah Capes MD MSc FRCPC and Vincent Woo MD FRCPC

PROCESS

Following the process used to develop previous Canadian Diabetes Association clinical practice guidelines (1,2), an Executive Committee, Steering Committee and Expert Committee with broad expertise and geographic representation were assembled. In total, 99 volunteer physicians and allied health professionals (including endocrinologists, family doctors, pediatricians, nephrologists, cardiologists, ophthalmologists, neurologists, urologists, diabetes nurse educators, dietitians, pharmacists, podiatrists, psychologists and other professionals, as well as researchers in a variety of disciplines) participated in the guideline development process.

The following basic principles were adopted to ensure that the values and empirical basis underlying each recommendation were explicitly identified, and to facilitate the critical scrutiny and analysis of each recommendation by other organizations and individuals.

- Each recommendation had to address a clinically important question related to 1 or more of the following: detection, prognosis, prevention or management of diabetes and its sequelae. Health benefits, risks and side effects of interventions were considered in formulating the recommendations.
- Whenever possible, each recommendation had to be justified by the strongest clinically relevant, empirical evidence that could be identified; the citation(s) reporting this evidence had to be noted adjacent to the relevant guideline.
- The strength of this evidence, based on prespecified criteria from the epidemiologic literature and other guidelines processes, had to be noted (3-8).
- This evidence had to be incorporated into a recommendation that was assigned a grade based on the available evidence, its methodological strength and its applicability to the Canadian population.
- Each recommendation had to be approved by the Steering Committee and Executive Committee, with 100% consensus.
- Guidelines based on biological or mechanistic reasoning, expert opinion or consensus had to be explicitly identified and graded as such.

IDENTIFYING AND APPRAISING THE EVIDENCE

At the outset of the process, and in order to ensure a consistent approach to the development of recommendations, committee members from each section of the guidelines attended a workshop on evidence-based methodology. Committee members identified clinically important questions related to diagnosis, prognosis, prevention and treatment of diabetes and its complications.

Authors were to explicitly define a) the population to which a guideline would apply; b) the test, risk factor or intervention being addressed; c) the “gold standard” test or relevant intervention to which the test or intervention in question was compared; and d) clinically relevant outcomes being targeted. This information was used to develop specific, clinically relevant questions that were the focus of literature searching. For each question, individual strategies were developed combining diabetes terms with methodological terms. A librarian with expertise in literature reviews performed a comprehensive search of the relevant English-language, published, peer-reviewed literature using validated search strategies (<http://hiru.mcmaster.ca/hedges/indexHIRU.htm>) of electronic databases (MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Trials and PsycINFO [where appropriate]). This was complemented by authors’ own manual and electronic searches. For topics that were covered in the 2003 guidelines, the literature searches focused on new evidence published since those guidelines. For new topics, the search time frame included the literature published since 1990, or earlier where relevant.

Key citations retrieved from the literature searches were then reviewed. Each citation that was used to formulate or revise a recommendation was assigned a level of evidence according to the prespecified criteria in Table 1, reflecting the methodological quality of the paper. When evaluating papers, authors were required to use standardized checklists that highlighted the most important elements of a well-conducted study. The level of evidence was then determined by the cited paper’s objectives, methodological rigour, susceptibility to bias and generalizability (Table 1). Because they could not be critically appraised, meeting abstracts, narrative review articles, news reports and other sources could not be used to support recommendations. Papers evaluating the cost-effectiveness of therapies or diagnostic tests were not included.

A number of considerations were made when evaluating the evidence within a given area. For example, people with diabetes are at high risk for several sequelae that are not exclusive to diabetes (e.g. cardiovascular diseases, renal failure and erectile dysfunction). As such, some evidence relating to these problems was identified that either excluded, did not report on, or did not focus on people with diabetes.

Whenever such evidence was identified, a level was assigned using the approach described above. Higher levels were assigned if a) people with diabetes comprised a predefined subgroup; b) the results in the diabetes subgroup were unlikely to have occurred by chance; and c) the evidence was generated in response to questions that were formulated prior to the analysis of the results.

Table 1. Criteria for assigning levels of evidence to the published studies

Level	Criteria
Studies of diagnosis	
Level 1	<ul style="list-style-type: none"> a) Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard) b) Independent interpretation of the diagnostic standard (without knowledge of the test result) c) Selection of people suspected (but not known) to have the disorder d) Reproducible description of both the test and diagnostic standard e) At least 50 patients with and 50 patients without the disorder
Level 2	Meets 4 of the Level 1 criteria
Level 3	Meets 3 of the Level 1 criteria
Level 4	Meets 1 or 2 of the Level 1 criteria
Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs <ul style="list-style-type: none"> a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators <ul style="list-style-type: none"> a) Patients were randomly allocated to treatment groups b) Follow-up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Nonrandomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Nonrandomized clinical trial or cohort study
Level 4	Other
Studies of prognosis	
Level 1	<ul style="list-style-type: none"> a) Inception cohort of patients with the condition of interest, but free of the outcome of interest b) Reproducible inclusion/exclusion criteria c) Follow-up of at least 80% of subjects d) Statistical adjustment for extraneous prognostic factors (confounders) e) Reproducible description of outcome measures
Level 2	Meets criterion a) above, plus 3 of the other 4 criteria
Level 3	Meets criterion a) above, plus 2 of the other criteria
Level 4	Meets criterion a) above, plus 1 of the other criteria

*In cases where such blinding was not possible or was impractical (e.g. intensive vs. conventional insulin therapy), the blinding of individuals who assessed and adjudicated study outcomes was felt to be sufficient

RCT = randomized controlled trial

GUIDELINE DEVELOPMENT

Expert Committee members evaluated the relevant literature, and guidelines were developed and initially reviewed by the Expert Committee. In the absence of new evidence since the publication of the 2003 clinical practice guidelines, recommendations from the 2003 document were not changed.

The studies used to develop and support each recommendation are cited beside the level of evidence. In some cases, each of the citations that supported a recommendation were not assigned the same level of evidence, but rather were of varying levels of evidence. In those circumstances, all relevant studies were cited, regardless of the grading assigned to the recommendation. The final grading depended on the overall evidence available, including the relative strengths of the studies from a methodological perspective and the studies' findings. Further details on the grading process are described below.

Finally, several treatment recommendations were based on evidence generated from the use of 1 therapeutic agent from a given class (e.g. 1 of the "statins"). Whenever evidence relating to 1 or more agents from a recognized class of agents was available, the recommendation was written so as to be relevant to the class, but specifically studied therapeutic agents were identified within the recommendation and/or cited reference(s). Only medications with Health Canada Notice of Compliance granted by February 18, 2008, were included in the recommendations.

GRADING THE RECOMMENDATIONS

After formulating new recommendations or modifying existing ones based on new evidence, each recommendation was assigned a grade from A through D (Table 2). The highest possible grade that a recommendation could have was based on the level of evidence. However, the assigned grading was lowered in some cases; for example, if the evidence was found not to be applicable to the Canadian population, or if based on the consensus of the Steering and Executive Committees, there were additional concerns regarding the recommendation. In some situations, the grading was also lowered for sub-

groups that were not well represented in the study, or in whom the beneficial effect of an intervention was less clear. Thus, a recommendation based on Level 1 evidence, deemed to be very applicable to Canadians and supported by strong consensus, was assigned a grade of A. A recommendation not deemed to be applicable to Canadians, or judged to require further supporting evidence, was assigned a lower grade. Where available, the number of patients that would need to be treated in order to prevent 1 clinical event (number needed to treat [NNT]) or to cause an adverse event (number needed to harm [NNH]) was considered in assessing the impact of a particular intervention. The degree to which evidence derived from other populations was felt to be relevant to diabetes was also reflected in the wording and grading of the recommendation. Finally, in the absence of Level 1, 2 or 3 supporting evidence, or if the recommendation was based on the consensus of the Steering and Executive Committees, the highest grade that could be assigned was D.

INTERPRETING THE ASSIGNED GRADE OF A RECOMMENDATION

The grade assigned to each recommendation is closely linked to the methodological rigour and robustness of the relevant clinical research. Therefore, as noted above, a high grade reflects a high degree of confidence that following the recommendation will lead to the desired outcome. Similarly, a lower grade reflects weaker evidence, and a greater possibility that the recommendation will change when more evidence is generated in the future. Of note, the assigned grade contains no subjective information regarding the importance of the recommendation or how strongly members of the committee felt about it; it contains information regarding only the evidence upon which the recommendation is based. Thus, many Grade D recommendations were deemed to be very important to the contemporary management of diabetes, based on clinical experience, case series, physiological evidence and current concepts of disease pathophysiology. However, the paucity of clinical evidence addressing the areas of therapy, prevention, diagnosis or prognosis precluded the assignment of a higher grade.

Clearly, clinicians need to base clinical decisions on the best available relevant evidence that addresses clinical situations. However, they are also frequently faced with having to act in the absence of clinical evidence, and there are many situations where good clinical evidence may be impossible, impractical or too expensive to generate (which implies that it would be impossible to develop Grade A recommendations). For example, it took the United Kingdom Prospective Diabetes Study (UKPDS) Group >20 years to collect and publish Level 1 evidence leading to a Grade A recommendation in support of the role of tight glycemic control to reduce microvascular disease in people with type 2 diabetes. Prior to the publication of the UKPDS results, the recommendation for glycemic control to prevent microvascular consequences

Grade	Criteria
Grade A	The best evidence was at Level 1
Grade B	The best evidence was at Level 2
Grade C	The best evidence was at Level 3
Grade D	The best evidence was at Level 4 or consensus

was a Grade B recommendation (1).

Varying grades of recommendations, therefore, reflect varying degrees of certainty regarding the strength of inference that can be drawn from the evidence in support of the recommendation. Therefore, these evidence-based guidelines and their graded recommendations are designed to satisfy 2 important needs: 1) the explicit identification of the best research upon which the recommendation is based, and an assessment of its scientific relevance and quality (captured by the assignment of a level of evidence to each citation); and 2) the explicit assignment of strength of the recommendation based on this evidence (captured by the grade). In this way, they provide a convenient summary of the evidence to facilitate clinicians' task of "weighting" and incorporating ever-increasing evidence into their daily clinical decision-making. They also facilitate the ability of clinicians, healthcare planners, healthcare providers and society in general to critically examine any recommendation and arrive at their own conclusions regarding its appropriateness. Thus, these guidelines facilitate their own scrutiny by others according to the same principles that they use to scrutinize the literature.

It is important to note that the system chosen for grading recommendations differs from the approach used in some other guideline documents, such as the one pertaining to the periodic health examination in Canada, in which harmful practices were assigned a grade of D (8). In this Canadian Diabetes Association guidelines document, recommendation to avoid any harmful practices would be graded in the same manner as all other recommendations. However, it should be noted that the authors of these guidelines focused on clinical practices that were thought to be potentially beneficial, and did not seek out evidence regarding the harmfulness of interventions.

EXTERNAL PEER REVIEW AND INDEPENDENT METHODOLOGICAL REVIEW

In July 2007, a draft document was circulated nationally and internationally for review by numerous stakeholders and experts in relevant fields. This input was then considered by the Executive and Steering Committees and revisions were made accordingly. Subsequently, a panel of 6 methodologists, who were not directly involved with the initial review and assessment of the evidence, independently reviewed each recommendation, its assigned grade and supportive citations. Based on this review, the wording, assigned level of evidence and grade of each recommendation were reassessed and modified as necessary. Revised recommendations were reviewed and approved by the Executive and Steering Committees. Selected recommendations were presented at a public forum at the Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism Professional Conference and Annual Meetings in Vancouver, British Columbia, in October 2007.

DISCLOSURE OF DUALITY OF INTEREST

Committee members were volunteers and received no remuneration or honoraria for their participation. Members of all committees signed an annual duality of interest form listing all financial interests or relationships with manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services. A full list of committee member disclosures is available online at <http://www.diabetes.ca>. Dualities of interest were also discussed during deliberations where relevant. In the case of a potential duality or outright conflict of interest, committee members removed themselves from discussions. Funding for the development of the guidelines was provided by the Canadian Diabetes Association and through unrestricted educational grants provided by the companies listed in the acknowledgements section (p. x). These companies were not involved in any aspect of guideline development, literature interpretation, the decision to publish or any other aspect related to the publication of these guidelines, and did not have access to guideline meetings, guideline drafts or committee deliberations.

GUIDELINE UPDATES

A process to update the full guidelines will commence within 5 years. Updates to individual chapters may be published sooner in the event of significant changes in evidence supporting the recommendations.

OTHER RELEVANT GUIDELINES

Introduction, p. S1.

ACKNOWLEDGEMENTS

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Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Ehud Ur MB FRCP

KEY MESSAGES

- The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs.
- A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose value of ≥ 11.1 mmol/L in a 75-g oral glucose tolerance test and best predicts the development of microvascular disease. This permits the diagnosis of diabetes to be made on the basis of the commonly available FPG test.
- The term “prediabetes” is a practical and convenient term for impaired fasting glucose and impaired glucose tolerance, conditions that place individuals at risk of developing diabetes and its complications.

DEFINITION OF DIABETES AND DYSGLYCEMIA

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidneys, eyes, nerves, heart and blood vessels.

Dysglycemia is a qualitative term used to describe blood glucose (BG) that is abnormal without defining a threshold. The adoption of this term reflects uncertainty about optimal BG ranges and the current understanding that cardiovascular (CV) risk and mortality risk exist in people with even slightly elevated BG levels.

CLASSIFICATION OF DIABETES

The classification of type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM) is summarized in Table 1. Appendix 1 addresses ideologic classification of diabetes.

DIAGNOSTIC CRITERIA

The diagnostic criteria for diabetes and the plasma glucose thresholds for other diagnostic categories are summarized in Tables 2 and 3 (1). These criteria are based on venous samples and laboratory methods.

Table 1. Classification of diabetes (1)

- **Type 1 diabetes*** encompasses diabetes that is primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.
- **Type 2 diabetes** may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.
- **Gestational diabetes mellitus** refers to glucose intolerance with onset or first recognition during pregnancy.
- **Other specific types** include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (Appendix 1).

*Includes latent autoimmune diabetes in adults (LADA), the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells (2)

Table 2. Diagnosis of diabetes

FPG ≥ 7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
Casual PG ≥ 11.1 mmol/L + symptoms of diabetes
Casual = any time of the day, without regard to the interval since the last meal
Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss
or
2hPG in a 75-g OGTT ≥ 11.1 mmol/L

A confirmatory laboratory glucose test (an FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. However, in individuals in whom type 1 diabetes is a possibility (younger individuals and lean, older individuals), to avoid rapid deterioration, confirmatory testing should not delay initiation of treatment.

2hPG = 2-hour plasma glucose

FPG = fasting plasma glucose

OGTT = oral glucose tolerance test

PG = plasma glucose

Diabetes

A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose (2hPG) value of ≥ 11.1 mmol/L in a 75-g oral glucose tolerance test (OGTT) and best predicts the development of microvascular disease (1). This permits the diagnosis of diabetes to be made on the basis of the commonly available FPG test. Although the frequency distributions of glycosylated hemoglobin (A1C) levels in some studies have characteristics similar to those obtained from FPG and 2hPG tests, the lack of standardization of the A1C test precludes its use in the diagnosis of diabetes.

Prediabetes

Elevated BG levels below the threshold for diabetes also have clinical consequences. The term “prediabetes” is a practical and convenient term for impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (Table 3), conditions that place individuals at risk of developing diabetes and its complications. It is important to stress that not all individuals with prediabetes will necessarily progress to diabetes. Indeed, a significant proportion of people who are diagnosed with IFG or IGT will revert to normoglycemia. People with prediabetes, particularly in the context of the metabolic syndrome (see below), would benefit from CV risk factor modification.

While people with IFG or IGT do not have the diabetes-associated risk for microvascular disease, they are at higher risk for the development of diabetes and CVD (3). IGT is more strongly associated with CVD outcomes. However, individuals identified as having both IFG and IGT are at high-

er risk for diabetes as well as CVD. Lifestyle interventions have been shown to be highly effective in delaying or preventing the onset of diabetes in people with IGT (4,5). Studies have not yet been done to examine CVD and total mortality.

There is no worldwide consensus on the definition of IFG (6,7). While the Canadian Diabetes Association continues to define IFG as an FPG value of 6.1 to 6.9 mmol/L (7), a number of limitations have been identified with regards to the existing lower limit of 6.1 mmol/L. These include suboptimal sensitivity for undiagnosed diabetes and IGT, and potential instability on retesting (due to the narrowness of the diagnostic range). For those individuals with an FPG value between 5.6 and 6.0 mmol/L and ≥ 1 risk factors for diabetes, consideration should be given to performing a 75-g OGTT (6-10).

Metabolic syndrome

Dysglycemia and type 2 diabetes are often manifestations of a much broader underlying disorder (11,12), including the metabolic syndrome – a highly prevalent, multifaceted condition characterized by a distinctive constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia, insulin resistance and dysglycemia. Individuals with the metabolic syndrome are at significant risk of developing diabetes and CVD. Evidence now exists to support an aggressive approach to identifying people with the metabolic syndrome and treating not only the hyperglycemia but also the associated CV risk factors, such as hypertension, dyslipidemia and abdominal obesity, in the hope of significantly reducing CV morbidity and mortality.

A lack of consensus exists regarding the operational definitions of the metabolic syndrome. In 1998, the World Health Organization (13) proposed a unifying definition that includes identification of the presence of insulin resistance. The United States (US) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) provided an operational definition based on ≥ 3 criteria that does not require a measure of insulin resistance (14,15). In the International Diabetes Federation (IDF) definition, the presence of abdominal obesity is a requisite risk factor. The IDF definition also provides ethnic-specific values for waist circumference (16). Table 4 presents the definitions of metabolic syndrome proposed by these 3 organizations. Data from the Third National Health and Nutrition Survey, which employed the 2001 ATP III criteria (15), showed that the overall prevalence of the metabolic syndrome in the US was approximately 20 to 25% (17).

Table 3. PG levels for diagnosis of IFG, IGT and diabetes

	FPG (mmol/L)		2hPG in the 75-g OGTT (mmol/L)
IFG	6.1–6.9		NA
IFG (isolated)	6.1–6.9	and	<7.8
IGT (isolated)	<6.1	and	7.8–11.0
IFG and IGT	6.1–6.9	and	7.8–11.0
Diabetes	≥ 7.0	or	≥ 11.1

2hPG = 2-hour plasma glucose

FPG = fasting plasma glucose

IFG = impaired fasting glucose

IGT = impaired glucose tolerance

OGTT = oral glucose tolerance test

NA = not applicable

PG = plasma glucose

Table 4. Definitions of the metabolic syndrome

	WHO (13)	NCEP ATP III 2001 (14) 2004 (15)		IDF (16)
Diagnostic criteria	Diabetes, IFG, IGT or insulin resistance (assessed by clamp studies) plus ≥ 2 other risk determinants are present	≥ 3 risk determinants are present		Central obesity (using ethnic-specific values) plus ≥ 2 other risk determinants are present (if BMI is >30 kg/m ² , central obesity can be assumed and WC does not need to be measured)
BG	Diabetes, IFG, IGT or insulin resistance	FPG ≥ 6.1 mmol/L	FPG ≥ 5.6 mmol/L	FPG ≥ 5.6 mmol/L (or previously diagnosed type 2 diabetes)
BP	$\geq 140/90$ mm Hg	$\geq 130/85$ mm Hg		$\geq 130/85$ mm Hg (or receiving treatment for previously diagnosed hypertension)
TG	≥ 1.7 mmol/L	≥ 1.7 mmol/L		≥ 1.7 mmol/L (or receiving treatment)
HDL-C	<0.9 mmol/L (men) <1.0 mmol/L (women)	<1.0 mmol/L (men) <1.3 mmol/L (women)		<1.0 mmol/L (men) <1.3 mmol/L (women) (or receiving treatment)
Abdominal obesity	Waist-to-hip ratio: >0.90 (men) >0.85 (women)	WC: >102 cm (men) >88 cm (women)		Europids / Sub-Saharan Africans / Eastern Mediterranean and Middle East (Arab) populations: WC ≥ 94 cm (men) WC ≥ 80 cm (women) South Asian / Malaysian / Asian / Indian / Chinese / Japanese / Ethnic South and Central American populations: WC ≥ 90 cm (men) WC ≥ 80 cm (women)
Kidney function	Urinary albumin excretion rate >20 μ g/min or ACR ≥ 30 mg/g	NA		NA

ACR = albumin to creatinine ratio

BG = blood glucose

BMI = body mass index

BP = blood pressure

FPG = fasting plasma glucose

HDL-C = high-density lipoprotein cholesterol

IDF = International Diabetes Federation

IFG = impaired fasting glucose

IGT = impaired glucose tolerance

NA = not applicable

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III

TG = triglycerides

WC = waist circumference

WHO = World Health Organization

OTHER RELEVANT GUIDELINES

Screening for Type 1 and Type 2 Diabetes, p. S14

Prevention of Diabetes, p. S17

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

RELEVANT APPENDIX

Appendix 1. Etiologic Classification of Diabetes Mellitus

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Screening for Type 1 and Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Ehud Ur MB FRCP, Jean-Louis Chiasson MD, Tom Ransom MD MSc FRCPC and Richard Rowe MBBS MAEd FRCPC

KEY MESSAGES

- In the absence of evidence for interventions to prevent or delay type 1 diabetes, screening for type 1 diabetes is not recommended.
- Screening for type 2 diabetes using a fasting plasma glucose (FPG) should be performed every 3 years in individuals ≥ 40 years of age.
- While the FPG is the recommended screening test, a 2-hour plasma glucose in a 75-g oral glucose tolerance test is indicated when the FPG is 6.1 to 6.9 mmol/L and may be indicated when FPG is 5.6 to 6.0 mmol/L and suspicion of type 2 diabetes or impaired glucose tolerance is high (e.g. for individuals with risk factors).

SCREENING FOR TYPE 1 DIABETES

Type 1 diabetes mellitus is primarily a result of pancreatic beta cell destruction due to an immune-mediated process that is likely incited by environmental factors in genetically predisposed individuals. An individual's risk of developing type 1 diabetes can be estimated by considering family history of type 1 diabetes with attention to age of onset and sex of the affected family members (1) and profiling immunity and genetic markers (2). The loss of pancreatic beta cells in the development of type 1 diabetes passes through a subclinical prodrome that can be detected reliably in first- and second-degree relatives of persons with type 1 diabetes by the presence of pancreatic islet autoantibodies in their sera (3). Given that the various serologic markers are not universally available, and in the absence of evidence for interventions to prevent or delay type 1 diabetes, no recommendations for screening for type 1 diabetes can be made.

SCREENING FOR TYPE 2 DIABETES

Adults

Undiagnosed type 2 diabetes may occur in $>2.8\%$ of the general adult population (4), with the number increasing to $>10\%$ in some populations (5,6). Tests for hyperglycemia can identify these individuals, many of whom will have or will be at risk for preventable diabetes complications (5,6). Although the relatively low prevalence of diabetes in the general population makes it unlikely that mass screening will be cost-effective, testing for diabetes in people with risk factors for type 2 diabetes or with diabetes-associated conditions is likely to

result in more benefit than harm and will lead to overall cost savings (7,8). Routine testing for type 2 diabetes is, therefore, justifiable in some but not all settings (9). Screening individuals as early as age 40 in family physicians' offices has proved to be useful in detecting unrecognized diabetes (10).

While fasting plasma glucose (FPG) is the recommended screening test, a 2-hour plasma glucose (2hPG) in a 75-g oral glucose tolerance test (OGTT) is indicated when the FPG is 6.1 to 6.9 mmol/L (11) and may be indicated when the FPG is 5.6 to 6.0 mmol/L and suspicion of type 2 diabetes or impaired glucose tolerance (IGT) is high (e.g. for individuals with risk factors listed in Table 1); see Figure 1.

As people with impaired fasting glucose (IFG) or IGT are at increased risk of developing type 2 diabetes and have an increased risk of macrovascular complications, the diagnosis of IGT, particularly in apparently healthy people, has impor-

Table 1. Risk factors for type 2 diabetes

- Age ≥ 40 years
- First-degree relative with type 2 diabetes
- Member of high-risk population (e.g. people of Aboriginal, Hispanic, South Asian, Asian or African descent)
- History of IGT or IFG*
- Presence of complications associated with diabetes
- Vascular disease (coronary, cerebrovascular or peripheral)*
- History of gestational diabetes mellitus
- History of delivery of a macrosomic infant
- Hypertension*
- Dyslipidemia*
- Overweight*
- Abdominal obesity*
- Polycystic ovary syndrome*
- Acanthosis nigricans*
- Schizophrenia[†]
- Other (see Appendix 1)

*Associated with insulin resistance

[†]The incidence of type 2 diabetes is at least 3 times higher in people with schizophrenia than in the general population (12,13). Using data collected in 1991, the prevalence of diabetes was assessed in $>20\,000$ individuals diagnosed with schizophrenia. The rate of diagnosed diabetes was 9 to 14%, exceeding rates for the general population prior to the widespread use of new antipsychotic drugs (14)

IFG = impaired fasting glucose

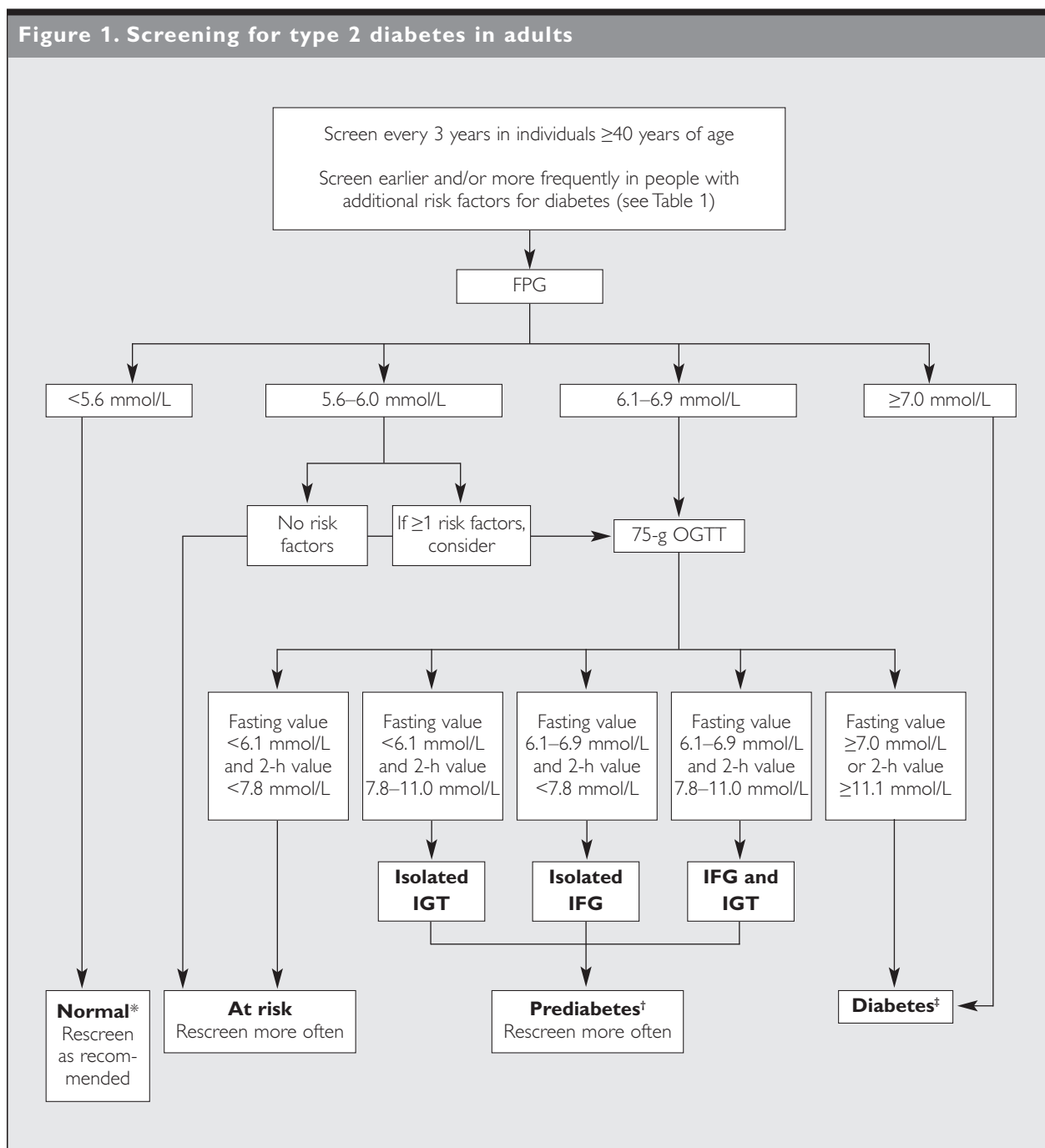
IGT = impaired glucose tolerance

tant prognostic implications (15). Classifying individuals with IFG and/or IGT, particularly in the context of the metabolic syndrome, identifies people who would benefit from cardiovascular risk factor reduction.

Risk scores

A number of risk scores based on clinical characteristics have been developed to identify individuals at high risk of having undiagnosed diabetes. However, the impact of known risk

Figure 1. Screening for type 2 diabetes in adults



*If, despite a normal fasting value, an OGTT is subsequently performed and the 2hPG value is 7.8–11.0 mmol/L, a diagnosis of isolated IGT is made

†Prediabetes = isolated IFG, isolated IGT, IFG and IGT (see Table 3 in "Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories," p. S10)

‡A confirmatory laboratory glucose test (either an FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done on another day in all cases in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
IFG = impaired fasting glucose

IGT = impaired glucose tolerance
OGTT = oral glucose tolerance test
PG = plasma glucose

factors on having undiagnosed type 2 diabetes differs between populations of different ethnic origins, and risk scores developed in Caucasian populations cannot be applied to populations of other ethnic groups (16).

RECOMMENDATIONS

1. All individuals should be evaluated annually for type 2 diabetes risk on the basis of demographic and clinical criteria [Grade D, Consensus].
2. Screening for diabetes using an FPG should be performed every 3 years in individuals ≥ 40 years of age [Grade D, Consensus]. More frequent and/or earlier testing with either an FPG or a 2hPG in a 75-g OGTT should be considered in people with additional risk factors for diabetes [Grade D, Consensus]. These risk factors include:
 - First-degree relative with type 2 diabetes
 - Member of high-risk population (e.g. people of Aboriginal, Hispanic, Asian, South Asian or African descent)
 - History of IGT or IFG
 - Presence of complications associated with diabetes
 - Vascular disease (coronary, cerebrovascular or peripheral)
 - History of gestational diabetes mellitus
 - History of delivery of a macrosomic infant
 - Hypertension
 - Dyslipidemia
 - Overweight
 - Abdominal obesity
 - Polycystic ovary syndrome
 - Acanthosis nigricans
 - Schizophrenia
 - Other risk factors (see Appendix 1)
3. Testing with a 2hPG in a 75-g OGTT should be undertaken in individuals with an FPG of 6.1 to 6.9 mmol/L in order to identify individuals with IGT or diabetes [Grade D, Consensus].
4. Testing with a 2hPG in a 75-g OGTT may be undertaken in individuals with an FPG of 5.6 to 6.0 mmol/L and ≥ 1 risk factors in order to identify individuals with IGT or diabetes [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories, p. S10

Prevention of Diabetes, p. S17

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

RELEVANT APPENDIX

Appendix 1. Etiologic Classification of Diabetes Mellitus

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Prevention of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Ehud Ur MB FRCP, Jean-Louis Chiasson MD, Tom Ransom MD MSc FRCPC and Richard Rowe MBBS MAEd FRCPC

KEY MESSAGES

- As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.
- Intensive and structured lifestyle modification that results in loss of approximately 5% of initial body weight can reduce the risk of progression from impaired glucose tolerance to type 2 diabetes by almost 60%.
- Progression from prediabetes to type 2 diabetes can also be reduced by pharmacologic therapy with metformin (~30% reduction), acarbose (~30% reduction) and thiazolidinedione (~60% reduction).

PREVENTION OF TYPE 1 DIABETES

Two major trials of interventions to prevent or delay the onset of type 1 diabetes have recently been completed. The European Nicotinamide Diabetes Intervention Trial (ENDIT), a randomized, double-blind, placebo-controlled trial of high-dose nicotinamide therapy, recruited first-degree relatives of people who were >20 years old when diagnosed with type 1 diabetes, islet cell antibody-positive, >40 years of age and had a normal oral glucose tolerance test (OGTT) result. Although nicotinamide had proved protective in animal studies, no effect was observed in the ENDIT study during the 5-year trial period (1).

The Diabetes Prevention Trial–Type 1 (DPT-1) studied the efficacy of low-dose insulin injections in high-risk (>50%) first-degree relatives of subjects with type 1 diabetes. Overall, the insulin treatments had no effect (2), but in a subset of participants with high levels of insulin auto-antibodies, a delay, and perhaps a reduction, in the incidence of type 1 diabetes was observed (3).

As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.

PREVENTION OF TYPE 2 DIABETES

Preventing type 2 diabetes would result in significant public health benefits, including lower rates of cardiovascular disease (CVD), renal failure, blindness and premature mortality. An epidemiologic analysis projected that if all diabetes

could be avoided in white American males through effective primary prevention, the risk of all-cause and cardiovascular mortality in the entire population could be reduced by up to 6.2 and 9.0%, respectively (4). Recent data from the US indicate that 28% of cardiovascular expenditures are attributable to diabetes (5).

Primary approaches to preventing diabetes in a population include the following: 1) programs targeting high-risk individuals in the community (such as those with impaired glucose tolerance [IGT] or obesity); 2) programs targeting high-risk subgroups of the population, such as high-risk ethnic groups; and 3) programs for the general population, such as those designed to promote physical activity and healthy eating in adults or children (6-8).

Prospective cohort studies have identified historical, physical and biochemical variables associated with the subsequent development of type 2 diabetes. These include older age, certain ethnic backgrounds, obesity (especially abdominal obesity), physical inactivity, history of gestational diabetes mellitus, overt coronary artery disease, high fasting insulin levels and IGT (9-11).

Results of large, well-designed studies assessing lifestyle and pharmacologic interventions in adults to prevent the progression from IGT to diabetes have been published.

Changes in lifestyle were assessed in the Finnish Diabetes Prevention Study (DPS) (12) and the Diabetes Prevention Program (DPP) (13). Dietary modification that targeted a low-calorie, low-fat, low-saturated fat, high-fibre diet and moderate-intensity physical activity of at least 150 minutes per week resulted in loss of approximately 5% of initial body weight. In both studies, the risk reduction for diabetes was 58% at 4 years. These studies included comprehensive, sustained programs to achieve these outcomes.

In another lifestyle intervention trial (14), 458 Japanese males with IGT were randomly assigned in a 4:1 ratio to a standard intervention (n=356) or an intensive intervention (n=102) and followed for 4 years. Intensive treatment was associated with a 67.4% reduction in risk of diabetes (p<0.001). IGT and diabetes were diagnosed using a 100-g OGTT and the following diagnostic criteria: IGT = 2-hour plasma glucose (2hPG) 8.8–13.1 mmol/L; diabetes = 2hPG ≥13.2 mmol/L. These levels have been shown to correspond to the WHO diagnostic criteria using a 75-g OGTT (15,16).

Metformin was used in a second arm of the DPP (13).

A dosage of 850 mg BID for an average of 2.8 years significantly decreased progression to diabetes by 31%. In the DPP population, metformin did not have any significant effect in the older age group (≥ 60 years) and in less obese (body mass index [BMI] < 35 kg/m²) subjects. To determine whether the observed benefit was a transient pharmacologic effect or more sustained, a repeat OGTT was undertaken after a short washout period. The results of this study suggested that 26% of the diabetes prevention effect could be accounted for by the pharmacologic action of metformin (which did not persist when the drug was stopped). After the washout, the incidence of diabetes was still reduced by 25% (17). The DPP Research Group recently published the results from the troglitazone arm, which was part of the original protocol (18). The drug was discontinued after a mean follow-up of 0.9 year due to liver toxicity. Troglitazone 400 mg OD resulted in a relative risk reduction of 75% ($p=0.02$) during the short period of time. This effect was not sustained after discontinuation of troglitazone.

The Study to Prevent Non Insulin Dependent Diabetes (STOP-NIDDM) used acarbose at a dosage of 100 mg TID in a 5-year study with a mean follow-up of 3.3 years (19). Overall, there was a 25% reduction in the risk of progression to diabetes when the diagnosis was based on 1 OGTT and a 36% reduction in the risk of progression to diabetes when the diagnosis was based on 2 consecutive OGTTs. This beneficial effect was not affected by age or BMI. However, when the drug was discontinued, the effect of acarbose did not persist (19). In this IGT population, acarbose treatment was also associated with a 49% reduction in CV events ($p=0.032$) and a 50% reduction in the progression of carotid intima-media thickness (20,21).

The Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study (22) examined the effect of orlistat in combination with an intensive lifestyle modification program (diet and exercise) on the prevention of diabetes in 3305 obese individuals. Subjects were randomized to orlistat 120 mg or placebo TID with meals for 4 years. Weight loss was observed in both groups, but the orlistat group lost significantly more (5.8 vs. 3 kg, $p<0.001$). Compared to placebo, orlistat treatment was associated with a further 37% reduction in the incidence of diabetes. However, 2 important methodological limitations affect the interpretation of these results. First, there was a very high dropout rate – 48% in the orlistat group and 66% in the placebo group. Second, the last observation carried forward was used for analysis, which is generally not favoured for prevention or survival studies. Nonetheless, the significant weight loss would be expected to decrease the risk of diabetes as already shown in the DPS and the DPP.

Most recently the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial (23,24) randomized 5269 subjects with IGT and/or impaired fasting glucose (IFG), in a 2x2 factorial fashion, to

ramipril (15 mg/day) and/or rosiglitazone (8 mg/day) vs. placebo. Eligible subjects were ≥ 30 years old and not known to have CVD. The primary outcome of DREAM was a composite of development of diabetes or death. The conclusion of the DREAM investigators was that the “results suggest an effect of ramipril on glucose metabolism, a finding that is consistent with other reports. For now, the routine use of ramipril for the express purpose of preventing diabetes is not indicated.” Treatment with rosiglitazone resulted in a 60% reduction in the primary composite outcome of diabetes or death (HR 0.40, 95% CI, 0.35–0.46), primarily due to a 62% relative reduction in the risk of progression to diabetes (HR 0.38, 95% CI, 0.33–0.44). Although the trial was not powered to provide a definitive estimate of the effect of rosiglitazone on CV outcomes, there was a trend toward an increase in risk of the CV composite outcome with rosiglitazone (HR 1.37, 95% CI, 0.97–1.94) driven primarily by a significant increase in nonfatal congestive heart failure (HR 7.03, 95% CI, 1.60–30.9, $p=0.01$). The final conclusion of the DREAM investigators was that “further work is needed to determine whether the beneficial effects seen with rosiglitazone will lead to a reduction in cardiovascular, renal, retinal, or other serious health consequences.”

RECOMMENDATIONS

1. A structured program of lifestyle modification that includes moderate weight loss and regular physical activity should be implemented to reduce the risk of type 2 diabetes in individuals with IGT [Grade A, Level 1A (12,13)] and IFG [Grade D, Consensus].
2. In individuals with IGT, pharmacologic therapy with a biguanide (metformin) [Grade A, Level 1A (13)] or an alpha-glucosidase inhibitor [Grade A, Level 1A (19)] should be considered to reduce the risk of type 2 diabetes. In individuals with IGT and/or IFG and no known cardiovascular disease, treatment with a thiazolidinedione could be considered to reduce the risk of type 2 diabetes [Grade A, Level 1A (23)].

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Organization of Diabetes Care

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Sora Ludwig MD FRCPC, Maureen Clement MD CCFP, Peggy Dunbar MEd PdT CDE and Jeffrey A. Johnson PhD

KEY MESSAGES

- Diabetes care depends upon the daily commitment of the person with diabetes to self-management practices with the support of an integrated diabetes healthcare (DHC) team.
- The DHC team should be multi- and interdisciplinary, and should establish and sustain a communication network among the health and community systems needed in the long-term care of the person with diabetes.
- Diabetes care should be systematic and, when possible, should incorporate organizational interventions such as electronic databases, automatic reminders for the patient and DHC team, to enable timely feedback.

INTRODUCTION

Diabetes care depends upon the daily commitment of the person with diabetes to self-management practices with the support of an integrated diabetes healthcare (DHC) team (1-3). Multifaceted interventions by a wide array of healthcare providers within the DHC team are needed to improve management, and should be supported by organizational interventions that promote regular diabetes monitoring and recall (4). Diabetes care should be founded on evidence-based clinical practice guidelines and be continuous, planned and equitable in terms of access. Diabetes programs and services should be community-based, culturally and socially appropriate, and respectful of age, gender and socioeconomic conditions.

DHC TEAM

The DHC team should be multi- and interdisciplinary. It should establish and sustain a communication network among the health and community systems needed in the long-term care of the person with diabetes (1-3,5-7). The person with diabetes and his or her family are central members of the DHC team. Family support has been shown to benefit the person with diabetes (8).

The core DHC team includes the family physician and/or specialist, and the diabetes educators (nurse and dietitian) (3,5-7). The membership of the team is extensive and includes numerous disciplines. A variety of individual and community healthcare supports, in particular psychological support, can improve glycemic control when part of usual

diabetes care (9). Flexibility in the operation of the DHC team is important. Changes in the core team, such as adding a team member, active participation by >1 discipline, and role expansion, have been shown to be associated with improved clinical outcomes (10,11).

The DHC team provides comprehensive, shared care that is collaborative in nature. This approach has been shown to increase the commitment and participation of the person with diabetes, and recognizes and enhances the role and practices of all members of the team (12-15).

The family physician's role is unique as the first, and at times, the principal medical contact for the person with diabetes. Family physicians can provide continuity of care for the person with diabetes, and provide care in the context of the family unit (16). This unique provider relationship can also provide opportunities to assist other family members who may be at risk for developing type 2 diabetes.

In some circumstances, this role may be shared with or assumed by a diabetes specialist (4,17,18). Studies suggest that diabetes-related outcomes are improved if medical care provided by the family physician is influenced by a diabetes specialist (18). This influence can vary from indirect input by the specialist as an opinion leader to direct involvement as part of a collaborative care model (4,19). Other effective interventions include the opportunity for input into quality-improvement working groups and direct feedback on processes and outcomes (20).

SELF-MANAGEMENT

Diabetes self-management is most effective when ongoing diabetes education and comprehensive care occur together (21-23). Effective diabetes self-management programs have been demonstrated to improve glycated hemoglobin (A1C) values (23-25).

Diabetes education must support self-management through approaches that promote informed, independent decisions relating to the individual's diabetes management. These approaches have been shown to improve patient adherence to treatment recommendations (26). Self-management education should include problem-solving, goal-setting and active participation in decision-making. This includes supporting the learner in interpreting and acting on the results of self-monitoring of blood glucose; making informed management decisions about insulin,

medication, nutrition, physical activity and other lifestyle issues; and including daily preventive practices such as good foot care.

The timing of referrals for self-management education should be based on the severity of presenting symptoms, the degree of metabolic control and the individual's understanding of immediate survival and safety skills and long-term management practices. Regular reinforcement through diabetes self-management education should be integrated into standard diabetes care (21,23).

Didactic programs alone should not be supported (27-28). In type 2 diabetes, group education has been shown to be as effective as individual education and promotes efficiency in delivery of diabetes self-management education programs (10,29,30). Ongoing rather than time-limited diabetes education sessions are beneficial in the long-term management of all forms of diabetes (31).

ORGANIZATIONAL INTERVENTIONS

A number of organizational interventions have been shown to improve the efficiency and effectiveness of the DHC team.

The DHC team should work within a structure that provides reminders and recall for diabetes metabolic control and complications risk assessment (3,32-35). Several studies have shown that the establishment of centralized computerized systems to monitor and remind both the person and the DHC team about appointments, investigations and interventions (including management changes and/or referrals) improves the diabetes care (35-37). Technological interventions including telemedicine are successful when the systems are designed to initiate timely actions (e.g. medication dosage changes in response to metabolic control markers) (38,39). Telephone feedback can be successful when the advice is individualized and specific (40). Internet-based programs, even with supports, have had mixed results (41).

Management systems with a population approach have been shown to have a positive impact on evidence-based care (42). Population-level clinical registries take an overview perspective to help deliver and monitor patient care, and allow an individual team member or the entire DHC team to assess key elements of care for a large group of patients. This approach can lead to both efficiencies in the use of existing resources and improvements in the overall level of care for a given patient population (42,43).

Case management or care coordination across a number of disciplines (primarily nursing, but also pharmacy and others) has been shown to improve the delivery of care. The role of diabetes case managers is most effective when integrated as part of a collaborative team (i.e. DHC team) and where the role of the team members is enhanced by focusing on the specific expertise of the discipline involved (e.g. a pharmacist's advice on medication adverse effects or interactions; a nurse educator's recommendations on medication selection and/or dosage adjustments) (44,45). Case management may

also improve clinical outcomes through the additional use of treatment algorithms and information systems (11,22,25,44-54). Case management is particularly successful when medication changes can be made in a timely fashion without the delay of waiting for physician approval (11).

DIABETES SYSTEMS ORGANIZATION

Diabetes has often been identified as the model for chronic disease management. Successful management of chronic disease requires more than the implementation of evidence-based clinical practice guidelines. It requires reframing existing community and healthcare systems. Unlike the approaches used to manage acute episodic illness, approaches to chronic disease require significant investment to create and support patients who are informed and engaged in their care and motivated practice teams (55-57). Innovative healthcare policy and delivery system redesign are required to fully support chronic disease management.

The United Kingdom, Australia and New Zealand have taken the lead in adopting models of chronic care (58-60). In Canada, British Columbia and Ontario have embraced an expanded chronic-care model that includes health promotion and prevention (49,61,62). Other provinces and territories are in various stages of discussion or adoption of chronic care models as a springboard for continued work within the primary-care and acute-care sectors.

Chronic disease management is usually framed within the context of the Chronic Care Model (CCM) (63-65). Adaptations of this model are reflected in the World Health Organization (WHO) Innovative Care for Chronic Conditions Framework and the Continuous Chronic Care Model (66). The CCM is a multifaceted, interdependent framework to improve healthcare delivery (55-57). It recognizes that the conventional acute healthcare delivery model must change to meet the needs of those with chronic illness within a system that is more inclusive and addresses healthcare from prevention to advanced management. The CCM identifies 6 interrelated components that are key to improving care (55): community resources and policy; health system organization of healthcare; self-management support; delivery-system design; decision support; and clinical information systems.

The CCM should be used as framework for continuous quality improvement. The effectiveness of the implementation of the CCM in primary-care settings in a multilevel, cluster-design randomized controlled trial (67) showed a mean decline in A1C of 0.6% ($p=0.008$). Other studies have examined the application of the CCM approach from local community health centres to a broader application in healthcare organizations and governmental jurisdictions. These studies support the broad application of the principles of the CCM, as well as implementation of specific aspects such as the use of self-management support and delivery system redesign (59,68,69).

RECOMMENDATIONS

1. Diabetes care should be organized around the person with diabetes using a multi- and interdisciplinary DHC team approach centred on self-care management [Grade B, Level 2 (3,11,23,24)].
2. Diabetes care should be systematic and incorporate organizational interventions such as electronic databases and clinical flow charts with automatic reminders for the patient and DHC team, to enable timely feedback for management changes [Grade B, Level 2 (3,11,35,36)].
3. The DHC team should facilitate the transfer of information among all members of the team as appropriate to ensure continuity of care and knowledge transfer [Grade B, Level 2 (11,70,71)].
4. Members of the DHC team should receive support and education, which can vary from indirect input to direct involvement from a diabetes specialist as part of a collaborative care model [Grade C, Level 3 (4,11,17-19)].
5. The role of DHC team members, including nurse educators [Grade B, Level 2 (11,44,51)], pharmacists [Grade B, Level 2 (11,44)] and dietitians [Grade B, Level 2 (51)], should be enhanced in cooperation with the physician to improve coordination of care. The DHC team should facilitate and/or implement timely diabetes management changes without unnecessary delay [Grade B, Level 2 (3)].
6. Case management or care coordination by health professionals with specialized training in diabetes should be considered for those individuals with difficult-to-manage diabetes [Grade B, Level 2 (11,50)].

OTHER RELEVANT GUIDELINES

Self-management Education, p. S25

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

Diabetes and Pregnancy, p. S168

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Self-management Education

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Self-management education (SME) that incorporates knowledge and skills development, as well as cognitive-behavioural interventions, should be implemented for all individuals with diabetes.
- The content of SME programs must be individualized according to the individual's type of diabetes, current state of metabolic stability, treatment recommendations, readiness for change, learning style, ability, resources and motivation.
- SME is a fundamental component of diabetes care and is most effective when ongoing diabetes education and comprehensive healthcare occur together.

INTRODUCTION

The objectives of diabetes self-management education (SME) are to increase the individual's involvement in, confidence with and motivation for control of their diabetes, its treatment and its effect on their lives (1). The term "SME," rather than "diabetes education," emphasizes the importance of including a variety of client-centred strategies and interventions that address the physical, psychological and social management of living with a chronic illness.

SME goes beyond a focus on adherence to guidelines and treatment prescriptions; it incorporates didactic and non-didactic (e.g. active, participatory) education, as well as social, behavioural and psychological interventions (2).

ELEMENTS OF SME

SME, which includes skills training, coping strategies, problem-solving and case management, has been demonstrated to improve the individual's ability to engage in effective self-care, lower glycated hemoglobin (A1C) levels and enhance quality of life (3-6). The essential components of SME are hypothesized to include: education tailored to individual needs

and circumstances; a group setting with others who share the same condition; feedback following an intervention; psychological emphasis in the intervention; and involvement of medical providers in providing the intervention (4). Long-term education with scheduled follow-up has also been shown to enhance the effect of education on glycemic control (7). Didactic programs alone are not advocated (3). Motivational interviewing, added to a behaviour-change program, may have greater impact (1,8).

The content and skill training components of SME programs must be individualized according to the type of diabetes, current state of metabolic stability, treatment recommendations, learning ability, ability to change, resources and motivation. Education should be offered in a timely and needs-based manner (5,9,10). Interventions that include face-to-face delivery, a cognitive-reframing teaching method and practical application content are more likely to improve glycemic control (9). The following basic knowledge areas are generally accepted as essential to an SME program (11,12), and each topic should include a problem-solving component; monitoring of relevant health parameters; healthy eating; physical activity; pharmacotherapy; hypo- and hyperglycemia prevention and management; and prevention and surveillance of complications and comorbid conditions. Suggested learning objectives for each topic area have been developed at basic, intermediate and advanced levels (Table 1) (11).

Skill training during SME should include self-monitoring of blood glucose (SMBG), making dietary choices, incorporating an exercise regimen, using medications as recommended and possible medication adjustment (5,9,10). For example, individuals with diabetes should be taught to interpret their own blood glucose (BG) meter results and make appropriate changes (5,13). Additional information regarding dietary choices, physical activity and BG levels before and after meals is frequently required to guide treatment decisions (13).

Table 1. Levels of learning (11)

Survival/basic level	<ul style="list-style-type: none"> • The knowledge, skills and motivation required for self-care to prevent, identify and treat the acute short-term complications of hyperglycemia or severe hypoglycemia • The person may or may not wish and/or need or be able to progress beyond this level
Intermediate level	<ul style="list-style-type: none"> • The knowledge, skills and motivation required for self-care to achieve recommended metabolic control, reduce the risk of long-term complications and facilitate the adjustment to living with diabetes
Advanced level	<ul style="list-style-type: none"> • The knowledge, skills and motivation required for self-care to support intensive diabetes management for optimal metabolic control, and full integration of care into the individual's life activities and goals

Interventions should focus on medications (including regimen changes and adherence), SMBG and physical activity to reduce A1C (10). For individuals with type 1 diabetes, education offered as part of intensified treatment interventions can result in long-lasting improvement in metabolic control and reduction in complications (14). Education for flexible insulin management and dietary freedom has been shown to improve quality of life as well as glycemic control (15,16).

EMPOWERMENT

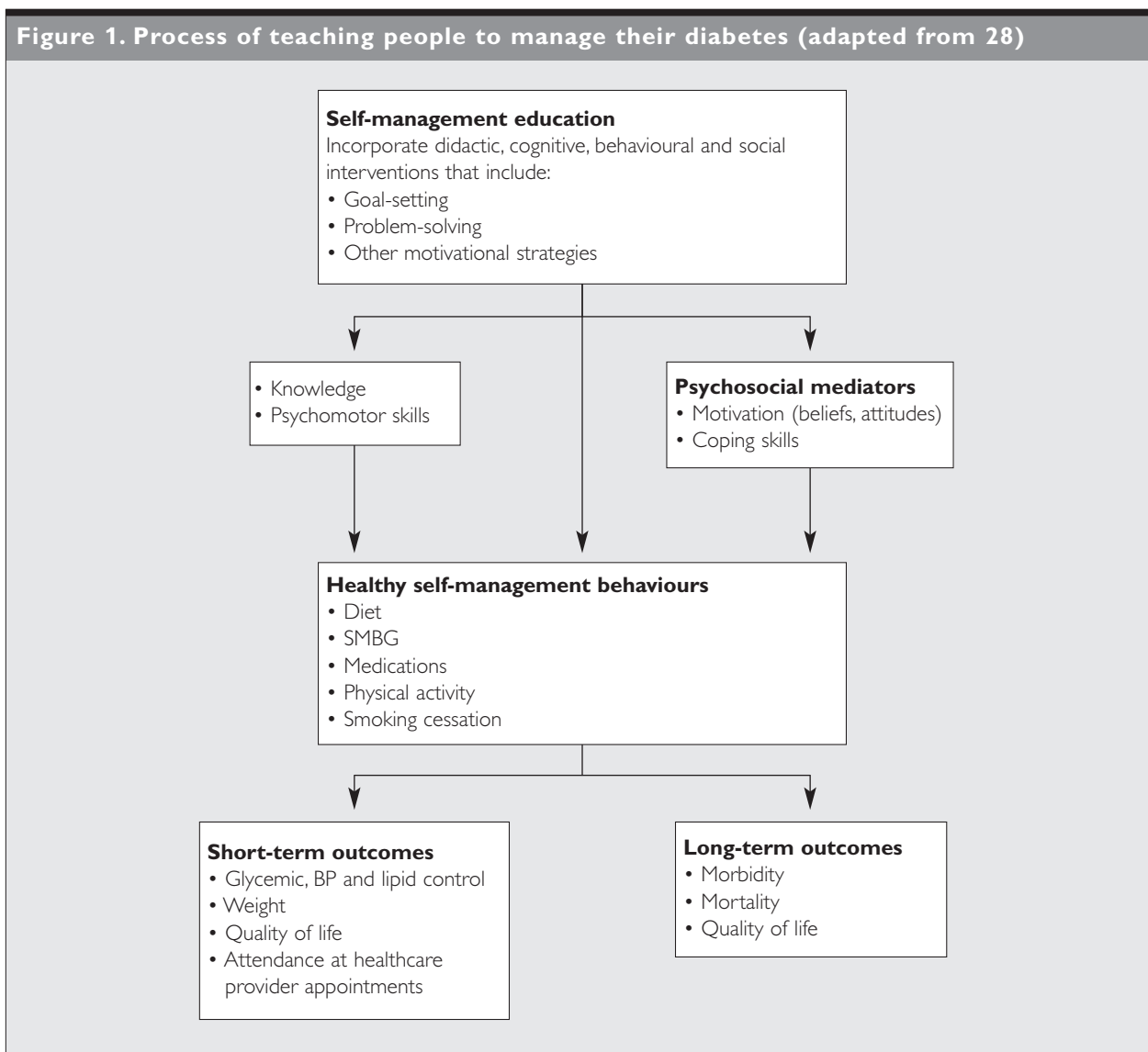
Empowerment is an essential psychological component of SME (17). To implement interventions using an empowerment approach and ensure informed decision making, the educator should engage in the following behaviours: demonstrate acceptance (respect) for the individual's perspectives; explore the affective or emotional aspect of an issue; work in an alliance or partnership with the individual; and facilitate active participation of all parties in the education process (18).

Approaches that increase an individual's participation and collaboration in decision making regarding care and education have been shown to be more effective than a didactic approach in enhancing psychological adjustment to diabetes and potentially preventing psychological distress (5,18-20).

SUPPORT SYSTEMS

Evidence suggests that including family members (parents, spouses, significant others) in educational interventions is beneficial for both children and adults in improving diabetes-related knowledge and glycemic control (20). Interventions that target families' ability to cope with stress or diabetes-related conflict are effective (20). Peer programs geared toward developing self-efficacy (i.e. self-confidence in one's ability to carry out a behaviour), sometimes referred to as "self-management" programs within the Chronic Disease Model, have demonstrated small improvements in psychological outcomes (21).

Figure 1. Process of teaching people to manage their diabetes (adapted from 28)



BP = blood pressure

SMBG = self-monitoring of blood glucose

EDUCATIONAL SETTINGS

SME conducted in community gathering places and group education settings has been shown to be effective in improving glycemic control in type 2 diabetes and promoting efficiencies in delivery of diabetes self-management programs (22,23). SME in home settings is also effective for adolescents with type 1 diabetes (9).

METHODS OF DELIVERY

Disease-specific chronic disease management models have demonstrated positive outcomes (4). Improved outcomes are also associated with integrated care, which includes case management (24,25). Diabetes self-management is most effective when ongoing diabetes education and comprehensive health-care occur together (5,14). Interactive health communications (computer-based information packages combined with either social, decision or behaviour-change support) have a largely positive effect on users and support improved behaviour and clinical outcomes (26,27).

CONCLUSION

While further study is required to define its most effective elements, SME is widely accepted as being essential in enhancing knowledge, skills and subsequent behavioural change. It has been shown to result in improved ability to handle the physical and emotional demands of self-care and in improved short- and long-term clinical outcomes (1-6,28). The key elements of effective SME are summarized in Figure 1.

RECOMMENDATIONS

1. People with diabetes should be offered timely diabetes education that is tailored to enhance self-care practices and behaviours [Grade A, Level 1A (5,9)].
2. All people with diabetes who are able should be taught how to self-manage their diabetes, including SMBG [Grade A, Level 1A (5)].
3. Self-management education that incorporates cognitive behavioural interventions such as problem-solving, goal-setting and self-monitoring of health parameters should be implemented in addition to didactic education programming for all individuals with diabetes [Grade B, Level 2 (3,9)].
4. Interventions that increase patients' participation and collaboration in healthcare decision-making should be used by providers [Grade B, Level 2 (5)].
5. SME interventions should be offered in small group and/or one-on-one settings, as both are effective for people with type 2 diabetes [Grade A, Level 1A (22,23)].
6. Interventions that target families' ability to cope with stress or diabetes-related conflict should be considered in education interventions when indicated [Grade B, Level 2 (20)].

OTHER RELEVANT GUIDELINES

Organization of Diabetes Care, p. S20
 Monitoring Glycemic Control, p. S32
 Psychological Aspects of Diabetes, p. S82
 Type 1 Diabetes in Children and Adolescents, p. S150

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Targets for Glycemic Control

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Optimal glycemic control is fundamental to the management of diabetes.
- Both fasting and postprandial plasma glucose levels correlate with the risk of complications and contribute to the measured glycated hemoglobin value.
- When setting treatment goals and strategies, consideration must be given to individual risk factors such as age, prognosis, presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycemia.

RELATIONSHIP BETWEEN BLOOD GLUCOSE LEVELS AND COMPLICATIONS OF DIABETES

Optimal glycemic control is fundamental to the management of diabetes. There is compelling evidence that improved glycemic control reduces risks of microvascular complications in both type 1 and type 2 diabetes (1-4). There is also evidence in patients with type 1 diabetes that improved glycemic control reduces the risk of cardiovascular disease (CVD) (5). However, similar benefit of improved glycemic control on macrovascular complications in people with type 2 diabetes has not been demonstrated through randomized controlled trials (4,6). In epidemiologic analyses, glycated hemoglobin (A1C) levels >7.0% are associated with a significantly increased risk of both microvascular and macrovascular complications, regardless of underlying treatment (3,7-9). The data from the Diabetes Control and Complications Trial (DCCT) (7) and the United Kingdom Prospective Diabetes Study (UKPDS) (8) demonstrated a continuous relationship between A1C and diabetes complications, with no apparent threshold of benefit. In the DCCT, a 10% reduction in A1C (e.g. from 8.0 to 7.2%) was associated with a 40 to 50% lower risk of retinopathy progression, although the absolute reduction in risk was substantially less at lower A1C levels (7). In the subsequent prospective follow-up of the DCCT cohort over 11 years, the risk of CVD and death from CV causes was reduced by 42 to 57% in the intensive insulin therapy group (5). In the UKPDS, this relationship was directly linear, with each 1.0% (absolute) reduction in mean A1C associated with a 37% decline in the risk of microvascular complications, a 14% lower rate of myocardial infarction

(MI) and fewer deaths from diabetes or any cause (8).

Both fasting plasma glucose (FPG) and postprandial PG levels correlate with the risk of complications. The analyses from the DCCT indicated that mean capillary glucose levels (based on both pre- and postprandial measurements) are also directly correlated to the risk of complications (10). FPG is directly related to CV events, with the increase in risk apparent even at PG levels that are within the normal range for people without diabetes (11). In a meta-analysis of 38 prospective studies, an FPG of >5.5 mmol/L was associated with an increased risk of CV events (12).

Postprandial hyperglycemia is a powerful predictor of adverse outcomes. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study found the 2-hour postchallenge PG to be a better predictor of CVD and all-cause mortality than FPG (13). This association between CV disease and 2-hour postprandial PG appears to be linear without a threshold (12,13). In another study, a 2-hour postprandial PG level >7.8 mmol/L was associated with an increase in all-cause mortality (14). The data from the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) also suggest that targeting postprandial PG with acarbose may reduce the risk of CV outcomes (15). There is also a strong association between postprandial hyperglycemia and microvascular complications. In a prospective observational study, postprandial hyperglycemia was found to be a better predictor of diabetic retinopathy than A1C (16). Similarly, in the Kumamoto study, the risk of microvascular complications increased with 2-hour postprandial PG levels >10.0 mmol/L (2). Additionally, the Diabetes Intervention Study found that in patients with type 2 diabetes, a 1-hour postprandial PG level ≤8.0 mmol/L conferred the lowest risk of MI or death, while levels >10.0 mmol/L were associated with the highest risk (17).

Despite the association between PG and CVD, 2 large, randomized, controlled, multicentre trials, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (5) and the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial (4) have shown that intensive glucose lowering in type 2 diabetes does not reduce major CV events.

The ACCORD trial recruited individuals with type 2 diabetes who were between the ages of 40 and 79 years and had CVD, or were between the ages of 55 and 79 years and had evidence

of significant atherosclerosis, albuminuria, left ventricular hypertrophy or at least 2 additional risk factors for CVD (obesity, hypertension, dyslipidemia or current status as a smoker). At baseline, mean age was 62.2 years, median duration of diabetes was 10 years and mean A1C was 8.3%. One of the major arms of the trial was to determine whether an intensive PG-lowering approach aimed at achieving A1C levels <6.0% would reduce CV events compared to a more conventional approach, aiming at achieving an A1C between 7.0 and 7.9%. After a mean 3.5 years of follow-up, the intensive treatment arm was halted because of safety concerns. The incidence of death was 11 per 1000 per year in the conventional treatment group (median achieved A1C of 7.5%) vs. 14 per 1000 per year in the intensive treatment group (median achieved A1C of 6.4%). Furthermore, intensive treatment was also associated with a significantly higher risk of severe hypoglycemia requiring medical assistance (3.1% in the intensive treatment group vs. 1.4% in the conventional treatment group) and weight gain. At the same time, there was evidence of a nonsignificant 10% reduction in the primary composite endpoint of nonfatal MI, stroke or CV death. The ADVANCE trial is a similar trial that enrolled individuals with type 2 diabetes who were at least 55 years of age and had a history of major macrovascular or microvascular disease or at least 1 other risk factor for vascular disease. At baseline, mean age was 66 years, mean duration of diabetes was 8 years and mean A1C was 7.48%. Intensive control with gli-clazide (modified release) based therapy (median achieved A1C of 6.5%) vs. the conventional treatment (which did not use gli-clazide-based treatment) (median achieved A1C of 7.3%) decreased nephropathy by 21% but did not decrease CV events. Similar to the ACCORD study, weight gain and severe hypoglycemia occurred more frequently in the intensive treatment group. The risk of hypoglycemia was 2.7% in the intensive treatment group, compared to 1.5% in the standard group. However, there was no increased risk of death in the intensively controlled group in the ADVANCE trial.

These trials suggest that in patients with type 2 diabetes and a CV risk profile similar to the ACCORD population, a strategy to target a normal A1C (i.e. <6.0%) may increase mortality. However, this risk must be balanced against the decrease in the incidence of nephropathy shown in the ADVANCE study, in which a similar population was treated with a strategy to target an A1C <6.5%.

Both FPG and postprandial PG values contribute to the A1C value. When the A1C values are higher (>8.5%), the major contribution is from the FPG levels, but as the A1C value approaches the target value of ≤7.0%, there is a greater contribution from the postprandial PG values (18,19). A recent study by Monnier and colleagues in 130 patients with type 2 diabetes using continuous glucose monitoring demonstrated that a 2-hour postprandial PG of <8.0 mmol/L correlates best with an A1C of <7.0% (20). In view of this, if A1C targets cannot be achieved with a postprandial target of

5.0 to 10.0 mmol/L, further postprandial BG lowering to 5.0 to 8.0 mmol/L can be considered (20).

RISK OF HYPOGLYCEMIA

While epidemiologic data suggest that the lowest risk of complications will occur in those with normoglycemia, the absolute benefit of lowering A1C levels from 7.0 to 6.5% is expected to be small and must be weighed against the risk of hypoglycemia. The hypoglycemia data from the DCCT showed that the risk of severe hypoglycemia was 3 times higher among participants receiving intensive therapy (1). Similarly, intensive therapy in type 2 diabetes increases the risk of severe hypoglycemia by 2-to-3 fold, particularly among those using insulin(3,4,6).

GLYCEMIC TARGETS

The glycemic targets recommended for most patients with type 1 and type 2 diabetes are listed in Table 1. However, clinical judgment is required to determine which people can reasonably and safely achieve these targets. Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors (e.g. the patient's age, prognosis, level of glycemic control, duration of diabetes, the presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycemia). To make the guidelines easier to incorporate into clinical practice, a single A1C target is provided, and PG targets have been rounded to whole numbers.

	A1C* (%)	FPG or preprandial PG (mmol/L)	2-hour postprandial PG (mmol/L)
Type 1 and type 2 diabetes	≤7.0	4.0–7.0	5.0–10.0 (5.0–8.0 if A1C targets not being met)

*Treatment goals and strategies must be tailored to the individual with diabetes, with consideration given to individual risk factors. Glycemic targets for children ≤12 years of age and pregnant women differ from these targets. See relevant guidelines for further details. An A1C of 7.0% corresponds to a laboratory value of 0.070. Where possible, Canadian laboratories should standardize their A1C values to Diabetes Control and Complications Trial levels (reference range: 0.040 to 0.060). However, as many laboratories continue to use a different reference range, the target A1C value should be adjusted based on the specific reference range used by the laboratory that performed the test. As a useful guide, an A1C target of 7.0% refers to a threshold that is approximately 15% above the upper limit of normal.

A1C = glycated hemoglobin
FPG = fasting plasma glucose
PG = plasma glucose

RECOMMENDATIONS

1. Glycemic targets must be individualized; however, therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve an A1C $\leq 7.0\%$ in order to reduce the risk of microvascular [Grade A, Level 1A (1-4)] and, in individuals with type 1 diabetes, macrovascular complications [Grade C, Level 3 (5)].
2. A target A1C of $\leq 6.5\%$ may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy [Grade A Level 1A (4)], but this must be balanced against the risk of hypoglycemia [Grade A Level 1A (4,5)] and increased mortality in patients who are at significantly elevated risk of cardiovascular disease [Grade A Level 1A (4)].
3. In order to achieve A1C of $\leq 7.0\%$, people with diabetes should aim for:
 - An FPG or preprandial PG target of 4.0 to 7.0 mmol/L [Grade B, Level 2 (1), for type 1; Grade B, Level 2 (2,3), for type 2 diabetes]; and
 - A 2-hour postprandial PG target of 5.0 to 10.0 mmol/L [Grade B, Level 2 (1), for type 1 diabetes; Grade B, Level 2 (2,3), for type 2 diabetes]. If A1C targets cannot be achieved with a postprandial target of 5.0 to 10.0 mmol/L, further postprandial BG lowering to 5.0 to 8.0 mmol/L can be considered [Grade D, Consensus, for type 1 diabetes; Grade D, Level 4 (18,19), for type 2 diabetes].

OTHER RELEVANT GUIDELINES

Monitoring Glycemic Control, p. S32

Hypoglycemia, p. S62

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

Diabetes and Pregnancy, p. S168

Diabetes in the Elderly, p. S181

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Monitoring Glycemic Control

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Glycated hemoglobin (A1C) is a valuable indicator of treatment effectiveness, and should be measured every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted.
- Awareness of all measures of glycemia, including self-monitoring of blood glucose (SMBG) results and A1C, provide the best information to assess glycemic control.
- The frequency of SMBG should be determined individually, based on the type of diabetes, the treatment prescribed, the need for information about BG levels and the individual's capacity to use the information from testing to modify behaviours or adjust medications.

GLYCATED HEMOGLOBIN TESTING

The Diabetes Control and Complications Trial (DCCT) (1) and the United Kingdom Prospective Diabetes Study (UKPDS) (2) demonstrated that glycated hemoglobin (A1C) and the development of long-term complications are correlated in both type 1 and type 2 diabetes, respectively. A1C is a reliable estimate of mean plasma glucose (PG) levels over the previous 3 to 4 months for most individuals (3). In uncommon circumstances where the rate of red blood cell turnover is significantly shortened or extended, or the structure of hemoglobin is altered, A1C may not accurately reflect glycemic status. A1C is a valuable indicator of treatment effectiveness and should be measured every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted. Testing at 6-month intervals may be considered in situations when glycemic targets are consistently achieved (4).

Currently, A1C is the preferred standard for assessing glycated hemoglobin, and laboratories are encouraged to use assay methods for this test that are standardized to the DCCT reference (4,5). A strong mathematical relationship between mean blood glucose (BG) values and A1C levels has been identified (6). In the future, A1C may be reported as "average blood glucose" in order to assist people to better understand the meaning of the results of this test (7).

SELF-MONITORING OF BLOOD GLUCOSE

Awareness of all measures of glycemia, including self-monitoring of blood glucose (SMBG) results and A1C, provide

the best information to assess glycemic control (4). Most people with diabetes can benefit from SMBG (8,9). Potential benefits, which may include improvement in A1C, avoidance and identification of hypoglycemia and increased lifestyle flexibility, are enhanced when individuals receive self-management education that enables them to adjust their dietary choices, physical activity and medication(s) in response to SMBG values (8,10-14). Effective education and implementation of strategies that employ patient empowerment and behaviour change theory may be most effective in supporting the incorporation of SMBG into the diabetes management routine (10,15-18).

Frequency of SMBG

The frequency of SMBG should be determined individually, based on the type of diabetes, the treatment prescribed, the need for information about BG levels and the individual's capacity to use the information from testing to modify behaviours or adjust medication.

For people with type 1 diabetes, SMBG is an essential component of daily diabetes management. In a large cohort study, performance of ≥ 3 self-tests per day was associated with a statistically and clinically significant 1.0% reduction in A1C levels (8). The results of multiple tests each day provide information that is better correlated to A1C than fasting results alone. BG measurements taken after lunch, after supper and at bedtime have demonstrated the highest correlation to A1C (6). More frequent testing is often required to provide the information needed to reduce hypoglycemia risk, adjust treatment and make appropriate lifestyle choices.

The benefits and optimal frequency of SMBG in type 2 diabetes are less clear than for type 1 (8,9,12,19-26). Current evidence is at times contradictory, and methodological and conceptual limitations exist in the literature. SMBG in those who are recently diagnosed, regardless of treatment, has been demonstrated to be of benefit (24). A large cohort study found that for people with type 2 diabetes treated with oral antihyperglycemic agents, testing at least once daily was associated with a 0.6% lower A1C than less frequent monitoring (8). A more recent randomized controlled trial (RCT) of SMBG with or without instruction on how to use results for diabetes self-management failed to demonstrate improvement in glycemic control (26). However, other adequately powered RCTs, large cohort studies and consensus state-

ments have identified benefits of more frequent testing on glycemic control, especially when this information is used to make appropriate and timely treatment and lifestyle adjustments (8,15,21,22,27,28). Given current uncertainties regarding the benefits of SMBG for individuals with type 2 diabetes not taking insulin, a well-designed RCT is needed to adequately answer this important but complex question.

For those with type 2 diabetes using insulin, frequent testing is also an integral component of care. In a large, nonrandomized study of individuals with stable type 2 diabetes using insulin, testing at least 3 times a day was associated with improved glycemic control (28).

In people with type 2 diabetes, timing of testing should take into account the potential for hypoglycemia associated with oral insulin secretagogues, and the fact that postprandial hyperglycemia is associated with increased cardiovascular risk (29). Postprandial PG results are generally better correlated to A1C than tests taken at other times of the day (30,31). In people with very poor glycemic control, however, fasting plasma glucose (FPG) may more strongly reflect overall glycemia (31).

Individuals who are intensively managed with multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII), with the goal of near normalization of BG levels, can use information obtained from preprandial and bedtime testing, as well as intermittent postprandial and nocturnal tests, to adjust insulin, dietary choices and activity levels. Testing before and after meals is associated with improved glycemic control compared to preprandial testing alone (32). Since nocturnal hypoglycemia may be more frequent in intensively managed individuals, periodic overnight testing at a time corresponding to peak insulin action should be undertaken (1,33-37).

Verification of accuracy of SMBG performance and results

Variability exists between BG results obtained using self-monitoring devices and laboratory testing of PG. At BG levels >4.2 mmol/L, a difference of $<20\%$ between fingertip sampling of capillary BG and simultaneous venous FPG levels is considered acceptable (5). Less variation is recommended for BG readings ≤ 4.2 mmol/L (5). In order to ensure accuracy of meter readings, meter results should be compared with laboratory measurement of PG at least annually and when indicators of glycemic control do not match meter readings. In addition, as errors in testing techniques are commonly observed, periodic re-education on correct monitoring technique may improve the accuracy of SMBG results (10,38). In rare situations, therapeutic interventions may interfere with the accuracy of some BG meter results. For example, icodextrin-containing peritoneal dialysis solutions may cause false high readings in some meters utilizing glucose dehydrogenase methods. To avoid unsafe treatment decisions, care should be taken to select an appropriate meter in these situations.

Alternate site testing

Meters are available that allow SMBG using blood samples from sites other than the fingertip, such as the forearm, palm of the hand or thigh. Accuracy of results over a wide range of BG levels and during periods of rapid change in BG levels is variable across sites. During periods of rapid change in BG levels (e.g. after meals, after exercise and during hypoglycemia), fingertip testing has been shown to more accurately reflect glycemic status than forearm or thigh testing (39,40). In comparison, blood samples taken from the palm near the base of the thumb (thenar area), demonstrate a closer correlation to fingertip samples at all times of day, and during periods of rapid change in BG levels (41,42).

KETONE TESTING

Ketone testing is recommended for all individuals with type 1 diabetes during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain elevated (>14.0 mmol/L) or when symptoms of diabetic ketoacidosis (DKA) such as nausea, vomiting or abdominal pain are present (4). If all of these conditions are present in type 2 diabetes, ketone testing should be considered, as DKA can also occur in these individuals.

During DKA, the equilibrium that is usually present between ketone bodies shifts toward formation of beta-hydroxybutyric acid (beta-OHB). As a result, testing methods that measure blood beta-OHB levels may provide more clinically useful information than those that measure urine acetoacetate or acetone levels. Assays that measure acetoacetate through urine testing may not identify the onset and resolution of ketosis as quickly as those that quantify beta-OHB levels in blood, since acetoacetate or acetone can increase as beta-OHB decreases with effective treatment (4,5). Meters that quantify beta-OHB from capillary sampling may be preferred for self-monitoring of ketones, as they have been associated with earlier detection of ketosis (4,43-45) and may provide information required to prevent progression to DKA. This may be especially useful for individuals with type 1 diabetes using CSII, as interruption of insulin delivery can result in rapid onset of DKA (46).

CONTINUOUS GLUCOSE MONITORING SYSTEMS

Continuous glucose monitoring systems (CGMS) measure glucose concentrations in the interstitial fluid. Two types of devices are available – newer systems that display “real time” glucose results directly on the monitoring system, and earlier “non-real time” (i.e. retrospective) devices that do not have this result display capability.

Real-time CGMS has been associated with positive outcomes, including improved A1C (47) and significantly reduced duration of hypoglycemia (48), hyperglycemia (48) and nocturnal hypoglycemia (48) in insulin-treated patients. Real-time CGMS results have been found to be closely correlated to BG

RECOMMENDATIONS

1. For most individuals with diabetes, A1C should be measured every 3 months to ensure that glycemic goals are being met or maintained. Testing at least every 6 months may be considered in adults during periods of treatment and lifestyle stability when glycemic targets have been consistently achieved [Grade D, Consensus].
2. For individuals using insulin, SMBG should be recommended as an essential part of diabetes self-management [Grade A, Level 1 (33), for type 1 diabetes; Grade C, Level 3 (8), for type 2 diabetes] and should be undertaken at least 3 times per day [Grade C, Level 3 (8,28)] and include both pre- and postprandial measurements [Grade C, Level 3 (6,28,32)]. In those with type 2 diabetes on once-daily insulin in addition to oral antihyperglycemic agents, testing at least once a day at variable times is recommended [Grade D, Consensus].
3. For individuals treated with oral antihyperglycemic agents or lifestyle alone, the frequency of SMBG should be individualized depending on glycemic control and type of therapy and should include both pre- and postprandial measurements [Grade D, Consensus].
4. In many situations, for all individuals with diabetes, more frequent testing should be undertaken to provide information needed to make behavioural or treatment adjustments required to achieve desired glycemic targets and avoid risk of hypoglycemia [Grade D, Consensus].
5. In order to ensure accuracy of BG meter readings, meter results should be compared with laboratory measurement of simultaneous venous FPG at least annually, and when indicators of glycemic control do not match meter readings [Grade D, Consensus].
6. Individuals with type 1 diabetes should be instructed to perform ketone testing during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain >14.0 mmol/L or in the presence of symptoms of DKA [Grade D, Consensus]. Blood ketone testing methods may be preferred over urine ketone testing, as they have been associated with earlier detection of ketosis and response to treatment [Grade B, Level 2 (44)].

values, although some discordance with BG levels during periods of hypoglycemia and significant hyperglycemia have been observed (48,49). Given the precision of current systems and the lag between changes in BG and interstitial glucose, particularly when BG levels are rapidly fluctuating (such as in the few hours after eating), CGMS readings may not reflect simultaneous BG values (50,51). As a result, CGMS technologies do not eliminate the need for capillary BG testing. Capillary tests must be performed both for the purposes of calibrating the device and for therapeutic decision-making.

With non-real time (i.e. retrospective) CGMS, glucose readings for intermittent time periods (usually 72 hours) are captured, but results are available only for retrospective viewing and analysis when data are downloaded to a computer. Non-real time (i.e. retrospective) CGMS has been associated with detection of unrecognized hypoglycemia in patients with either type 1 or type 2 diabetes (52,53), detection of unexpected hyperglycemia in women with gestational diabetes mellitus (54), reduction in the duration of hypoglycemia in insulin-treated patients (55) and less frequent hypoglycemia in a pediatric, insulin-treated population (53). It is not yet clear if use of non-real time technology reduces A1C values (49,53,55,56). Discrepancies in non-real time CGMS accuracy have been identified (46,57-60), especially during hypoglycemia (57,58) and nocturnally (59,60).

The scarcity of data (including accuracy data) presently available precludes making definitive recommendations regarding the role of real-time CGMS in diabetes management. However, given its rapidly increasing use, it is incumbent upon healthcare providers involved in the management of people with diabetes (particularly type 1 diabetes) to be aware of this technology.

OTHER RELEVANT GUIDELINES

Self-management Education, p. S25
 Targets for Glycemic Control, p. S29
 Physical Activity and Diabetes, p. S37
 Insulin Therapy in Type 1 Diabetes, p. S46
 Hypoglycemia, p. S62
 Hyperglycemic Emergencies in Adults, p. S65
 Type 1 Diabetes in Children and Adolescents, p. S150
 Type 2 Diabetes in Children and Adolescents, p. S162
 Diabetes and Pregnancy, p. S168

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Physical Activity and Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women and in both type 1 and type 2 diabetes.
- Before beginning a program of physical activity more vigorous than walking, people with diabetes should be assessed for conditions that might be contraindications to certain types of exercise, predispose to injury or be associated with increased likelihood of cardiovascular disease.
- Structured physical activity counselling by a physician or skilled healthcare personnel or case managers has been very effective in increasing physical activity, improving glycemic control, reducing the need for antihyperglycemic agents and insulin, and producing modest but sustained weight loss.

BENEFITS OF PHYSICAL ACTIVITY

Physical activity can help people with diabetes achieve a variety of goals, including increased cardiorespiratory fitness, increased vigour, improved glycemic control, decreased insulin resistance, improved lipid profile and maintenance of weight loss (1,2). The terms “physical activity” and “exercise” are used interchangeably in this chapter.

A systematic review and meta-analysis found that supervised programs involving aerobic or resistance exercise improved glycemic control in adults with type 2 diabetes (3). In contrast, most clinical trials evaluating exercise interventions in people with type 1 diabetes have not demonstrated a beneficial effect of exercise on glycemic control (4).

Moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women and in both type 1 and type 2 diabetes. Large cohort studies have demonstrated that in people with type 2 diabetes, regular physical activity (5-7) and/or moderate to high cardiorespiratory fitness (8) are associated with reductions in cardiovascular and overall mortality of 39 to 70% over 15 to 20 years of follow-up. A cohort study in people with type 1 diabetes found that 7-year mortality was 50% lower in those reporting ≥ 2000 kcal of weekly exercise (equivalent to ≥ 7 hours per week of brisk walking) compared to those reporting < 1000 kcal of

physical activity per week (9). Aerobic exercise increases cardiorespiratory fitness in both type 1 and type 2 diabetes (10), and has recently been shown to limit the development of peripheral neuropathy (11).

EXERCISE CONSIDERATIONS IN PEOPLE WITH DIABETES

People with diabetes should be informed that regular exercise is a key part of their treatment plan. Before beginning a program of physical activity more vigorous than walking, people with diabetes should be assessed for conditions that might be contraindications to certain types of exercise, predispose to injury or be associated with increased likelihood of cardiovascular disease (CVD). Examples of such conditions would include severe autonomic neuropathy, severe peripheral neuropathy, and preproliferative or proliferative retinopathy, all of which require treatment prior to commencement of vigorous exercise. An exercise electrocardiogram (ECG) stress test should be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to undertake exercise more vigorous than brisk walking. Previously sedentary individuals may have to gradually build up their amount of exercise, starting with as little as 5 to 10 minutes per day. Multiple, shorter exercise sessions (each lasting at least 10 minutes) in the course of a day should be considered, as this regimen is probably as useful as a single longer session of equivalent length and intensity (12,13).

Studies have demonstrated a role for both aerobic and resistance exercise in suitable people with diabetes (Table 1, Table 2). Walking is the most popular and most feasible type of aerobic exercise in most overweight middle-aged and elderly people with diabetes. For most middle-aged individuals, moderately brisk walking on level ground would be an example of moderate aerobic exercise, while brisk walking up an incline or jogging would be vigorous aerobic exercise. Resistance exercise performed 2 or 3 times per week may provide benefits that complement those of aerobic training (e.g. increased strength and vigour, reduced body fat and increased resting metabolic rate) (3,14). The studies reporting the greatest impact of resistance exercise on glycated hemoglobin (A1C) have had subjects progress to 3 sets (with approximately 8 repetitions per set) of resistance-type exercises at relatively high intensity (i.e. the maximum weight that

Table 1. Aerobic exercise

Definition and recommended frequency	Intensity	Examples
Rhythmic, repeated and continuous movements of the same large muscle groups for at least 10 minutes at a time	Moderate: 50–70% of person's maximum heart rate	<ul style="list-style-type: none"> • Biking • Brisk walking • Continuous swimming • Dancing • Raking leaves • Water aerobics
Recommended for a minimum of 150 minutes per week (moderate intensity)	Vigorous: >70% of person's maximum heart rate	<ul style="list-style-type: none"> • Brisk walking up an incline • Jogging • Aerobics • Hockey • Basketball • Fast swimming • Fast dancing

Table 2. Resistance exercise

Definition	Recommended frequency	Examples
Activities that use muscular strength to move a weight or work against a resistant load*	3 times per week <ul style="list-style-type: none"> • Start with 1 set of 10–15 repetitions at moderate weight • Progress to 2 sets of 10–15 repetitions • Progress to 3 sets of 8 repetitions at heavier weight 	<ul style="list-style-type: none"> • Exercise with weight machines • Weight lifting

*Initial instruction and periodic supervision are recommended

can be lifted 8 times), 3 times per week (15,16) or more (17). The effects of resistance exercise and aerobic exercise are additive (18). Individuals who wish to begin resistance exercise should receive initial instruction and periodic supervision by a qualified exercise specialist.

During and after all but the most intense exercise, blood glucose tends to decline due to increased glucose disposal and insulin sensitivity (19). However, during and especially after brief, very intense exercise (e.g. competitive track and field, hockey, basketball, intense resistance training), blood glucose will rise as a result of increases in glucose production that exceed increases in glucose disposal (20). Exercise late in the day can be associated with increased risk of overnight hypoglycemia in people with type 1 diabetes (21). In type 1 diabetes, small studies have explored 3 types of strategies for the prevention of hypoglycemia using protocols that generally involve postprandial exercise. These strategies include the consumption of extra carbohydrates for exercise (22), limiting preprandial bolus insulin doses (23) or altering basal insulin for insulin pump users (24). These strategies can be used alone or in combination (25).

Despite a strong body of evidence supporting the health benefits of lifestyle modification in people with type 2 diabetes, application in medical care settings remains a challenge (26). Healthcare professionals can heighten awareness of the importance of physical activity by promoting regular exercise as a key component of therapy and identifying resources in the community (27). Structured physical activity counselling by a physician (28) or skilled healthcare personnel or case managers (29,30) has been very effective in increasing physical activity, improving glycemic control (29), reducing the need for oral antihyperglycemic agents and insulin (30), and producing modest but sustained weight loss (31).

RECOMMENDATIONS

1. People with diabetes should accumulate a minimum of 150 minutes of moderate- to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise [Grade B, Level 2, for type 2 diabetes (3); Grade C, Level 3, for type 1 diabetes (9)].
2. People with diabetes (including elderly people) should also be encouraged to perform resistance exercise 3 times per week [Grade B, Level 2 (15,16)] in addition to aerobic exercise [Grade B, Level 2 (18)]. Initial instruction and periodic supervision by an exercise specialist are recommended [Grade D, Consensus].
3. An exercise ECG stress test should be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to undertake exercise more vigorous than brisk walking [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Monitoring Glycemic Control, p. S32

Insulin Therapy in Type 1 Diabetes, p. S46

Hypoglycemia, p. S62

Identification of Individuals at High Risk of Coronary Events, p. S95

Screening for the Presence of Coronary Artery Disease, p. S99

Vascular Protection in People With Diabetes, p. S102

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Nutrition Therapy

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KEY MESSAGES

- Nutrition therapy can reduce glycated hemoglobin by 1.0 to 2.0% and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes.
- Consistency in carbohydrate intake, and spacing and regularity in meal consumption may help control blood glucose and weight.
- Replacing high-glycemic index carbohydrates with low-glycemic index carbohydrates in mixed meals has a clinically significant effect on glycemic control in people with type 1 or type 2 diabetes.

INTRODUCTION

Nutrition therapy is an integral part of the treatment and self-management of diabetes. The goals of nutrition therapy are to maintain or improve quality of life and nutritional and physiological health, and to prevent and treat acute and long-term complications of diabetes, associated comorbid conditions and concomitant disorders.

It is well documented that nutrition therapy can improve glycemic control (1) by reducing glycated hemoglobin (A1C) by 1.0 to 2.0% (2-4) and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes (2-4). Counselling provided by a registered dietitian with expertise in diabetes management (5,6), either delivered in a small group and/or individual setting (7-9), has demonstrated benefits for those with, or at risk for, diabetes. Nutrition therapy should be based on individual needs, be regularly evaluated and reinforced in an intensive manner (10-12), and be part of self-management education programs (13).

As evidence is limited for the rigid adherence to any single dietary prescription (14,15), nutrition therapy and meal planning should be individualized to accommodate the person's preferences, age, needs, culture, lifestyle, economic status (16), activity level and readiness to change. In general, people with diabetes should follow the healthy diet recommended for the general population in *Eating Well with Canada's Food Guide* (17). This involves consuming a variety of foods from the 4 food groups (vegetables and fruits; grain products; milk and alternatives; meat and alternatives). Foods should be low in energy density to optimize satiety and discourage overconsumption, help attain and maintain a

healthy body weight, and ensure an adequate intake of carbohydrate, fibre, protein, essential fatty acids, vitamins and minerals.

Consistency in carbohydrate intake (18), and spacing and regularity in meal consumption may help control blood glucose (BG) levels (13,18,19). Inclusion of snacks as part of a person's meal plan should be individualized based on meal spacing, metabolic control, treatment regimen and risk of hypoglycemia, and should be balanced against the potential risk of weight gain (20,21).

CARBOHYDRATE

Individuals using insulin therapy should adjust their insulin based on the carbohydrate content of their meals. Intensive insulin therapy regimens that include multiple injections of rapid-acting insulin matched to carbohydrate allow for flexibility in meal size and frequency (22,23). Improvements in BG and quality of life can be achieved when individuals with type 1 diabetes receive education on matching insulin to carbohydrate content (e.g. carbohydrate counting) (24,25). In doing so, dietary fibre should be subtracted from total carbohydrate. The acceptable macronutrient distribution range, or percentage of total daily energy associated with reduced risk of chronic disease for adults, is as follows: carbohydrate intake of no less than 45% (in part to prevent high intakes of fat); and fat intake of a maximum of 35% (26). Diets that provide >60% of total daily energy from low-glycemic-index and high-fibre carbohydrates improve glycemic and lipid control in adults with type 2 diabetes (27).

Replacing high-glycemic-index carbohydrates with low-glycemic-index carbohydrates in mixed meals has a clinically significant effect on glycemic control in people with type 1 or type 2 diabetes (28-32). Dietary advice aimed at increasing the use of low-glycemic-index foods can help improve glycemic control in people with type 1 diabetes by reducing A1C and the number of hypoglycemic episodes (29,33). Choosing low-glycemic-index foods within the same category of food may help improve glycemic control in insulin-resistant individuals with type 2 diabetes (29). The decision to teach a person to use the glycemic index should be based on the individual's interest and ability.

Evidence suggests that the addition of soluble dietary fibre (e.g. eggplant, okra, oat products, beans, psyllium and barley) slows gastric emptying and delays the absorption of

glucose in the small intestine, thereby improving postprandial BG control (34). In addition, cohort studies demonstrate that diets high in dietary fibre, especially cereal fibre, are associated with a decreased risk of cardiovascular disease (CVD) (35). Due to the recognized beneficial effects of dietary fibre intake in people with diabetes, higher intakes than those recommended for the general population are recommended for adults with diabetes (25 to 50 g/day) (36).

Sucrose

Sucrose intake of up to 10% of total daily energy (e.g. 50 to 65 g/day in a 2000 to 2600 kcal/day diet) is acceptable, as there is no evidence that sucrose intake up to this level has any deleterious effect on glycemic control or lipid profile in people with type 1 or type 2 diabetes (37-39). Intake of sucrose >10% of total daily energy may increase BG and triglycerides (TG) levels in some individuals (40,41).

Fructose

Consumption of up to 60 g of added fructose (e.g. fructose-sweetened beverages or foods) per day in place of an equal amount of sucrose is unlikely to have any harmful effect in most people with diabetes (42). Fructose has been shown to improve the capacity of hyperglycemia to suppress hepatic glucose production in type 2 diabetes (43). However, fructose has no definite advantage over sucrose in long-term use. Consumption of >60 g of added fructose per day by people with diabetes is not recommended, as it may increase circulating TG levels (44).

Sugar alcohols

Sugar alcohols (maltitol, mannitol, sorbitol, lactitol, isomalt and xylitol) vary in the degree to which they are absorbed. The conversion rate is slow, variable, usually minimal and may have no significant effect on BG. Matching rapid-acting insulin to the intake of sugar alcohols is not recommended (45). Consumption of >10 g/day may produce adverse gastrointestinal symptoms in some individuals (46). Although there are no long-term studies of consumption of sugar alcohols by people with diabetes, consumption of up to 10 g/day by people with diabetes does not appear to result in adverse effects (47).

Sweeteners

Acesulfame potassium, aspartame, cyclamates, saccharin and sucralose have been approved by Health Canada, and all have been shown to be safe when used by people with diabetes (Table 1) (47). While the safety of sweeteners in pregnancy has not been rigorously studied, based on their history of use and lack of reported adverse effects during pregnancy and lactation (48), acesulfame potassium, aspartame and sucralose may be consumed within the acceptable daily intake limits. Saccharin and cyclamates are not recommended during pregnancy and lactation because of a lack of evidence for their safety (47,48).

Table 1. Acceptable daily intake* of sweeteners (47)

Sweetener	Acceptable daily intake (mg/kg body weight)
Acesulfame potassium	15
Aspartame	40
Cyclamate	11
Saccharin	5
Sucralose	9

*Defined as the amount of sweetener that can be safely consumed on a daily basis over a person's lifetime without any adverse effects

PROTEIN

There is no evidence to suggest that the usual recommended protein intake (15 to 20% of total daily energy) needs to be modified for people with diabetes. Essential amino acids are toxic in excess (49), when intake is at a rate that exceeds the body's capacity to eliminate the end products of their metabolism.

FAT

Current recommendations for the general population to limit fat intake to <35% of energy (26) apply equally to people with diabetes and prediabetes. As the risk of coronary artery disease (CAD) in people with diabetes is 2 to 3 times that of those without diabetes, saturated fats should be restricted to <7% of total energy daily intake (50) and trans fatty acids should be kept to a minimum. Polyunsaturated fats should be limited to <10% of total energy intake (51). Meal plans should favour monounsaturated fats, when possible, and include foods rich in polyunsaturated omega-3 fatty acids (e.g. fatty fish) and plant oils (e.g. canola, walnut, flax). In secondary prevention trials, omega-3 fatty acids from both plant (alpha-linolenic acid) and marine (eicosapentaenoic acid and docosahexaenoic acid) sources have demonstrated significant cardioprotective effects (52). In a prospective cohort study of women with type 2 diabetes, higher consumption (1 to 3 servings per month) of omega-3 fatty acids from fish was associated with a 40% reduction in CAD compared to those with a low intake (<1 serving per month) (53). Those who consumed fatty fish >5 times per week had a 64% reduction in CAD compared with those in the low-intake category (53). Flexibility regarding total fat intake may be appropriate. For example, if an individual's fat intake is primarily composed of mono- and polyunsaturated fats and is low in trans fatty acids arising from industrial hydrogenation, a higher fat intake (i.e. 35% of total daily energy) may be justified (54-57).

VITAMIN AND MINERAL SUPPLEMENTS

People with diabetes should be encouraged to meet their nutritional needs by consuming a well-balanced diet. Routine vitamin and mineral supplementation is generally not recommended. Antioxidant supplements (vitamin E, vitamin C or beta-carotene) have not demonstrated benefits in CVD outcomes or glycemic control (58-60). As there is evidence that long-term beta-carotene supplementation may be harmful in smokers, antioxidant supplementation should be discussed with patients who smoke (59,61). Supplementation with 10 µg (400 IU) vitamin D is recommended in people >50 years of age. Supplementation with folic acid (400 µg) is recommended in women who could become pregnant (17). There is no evidence that dietary supplements such as meal replacements, specialty bars or formulas designed for diabetes are needed for glycemic control. No studies have identified which foods they displace from the diet.

ALCOHOL

The same recommendations regarding alcohol consumption in the general population apply to people with diabetes (i.e. ≤2 standard drinks per day and ≤14 standard drinks per week for men, and ≤9 per week for women) (62,63). Moderate amounts of alcohol (1 to 2 standard drinks) consumed with food do not cause acute hyperglycemia or hypoglycemia, and do not require subtracting food from the usual meal plan (Table 2).

Table 2. Examples of standard alcoholic drinks

Drink	Ethanol content (%)	Quantity (mL)
Beer	5	341 (12 oz)
Table wine	12	142 (5 oz)
Spirits	40	43 (1.5 oz)
Fortified wine (e.g. sherry, port)	18	85 (3 oz)

Caution must be exercised to prevent hypoglycemia secondary to alcohol consumption in people with type 2 diabetes, particularly the fasted elderly who are using insulin and/or insulin secretagogues (64). For people with type 1 diabetes, moderate consumption of alcohol with, or 2 or 3 hours after, the previous evening meal may result in hypoglycemia the next morning after breakfast and as late as 24 hours after alcohol consumption (65,66). Alcohol ingestion may mask the symptoms of hypoglycemia (67), reduce hepatic production of glucose and impair an individual's judgement.

NUTRITIONAL CONSIDERATIONS

A summary of nutritional considerations for people with diabetes is shown in Table 3.

RECOMMENDATIONS

1. Nutrition counselling by a registered dietitian is recommended for people with diabetes to lower A1C levels [Grade B, Level 2 (3), for type 2 diabetes; Grade D, Consensus, for type 1 diabetes]. Nutrition education is equally effective when given in a small group or one-on-one setting [Grade B, Level 2 (9)].
2. Individuals with diabetes should be encouraged to follow *Eating Well with Canada's Food Guide* in order to meet their nutritional needs [Grade D, Consensus].
3. People with type 1 diabetes should be taught how to match insulin to carbohydrate intake [Grade B, Level 2 (23)] or should maintain consistency in carbohydrate intake [Grade D, Level 4 (18)]. People with type 2 diabetes should be encouraged to maintain regularity in timing and spacing of meals to optimize glycemic control [Grade D, Level 4 (19)].
4. People with type 1 or type 2 diabetes should choose food sources of carbohydrates with a low glycemic index, rather than a high glycemic index, more often to help optimize glycemic control [Grade B, Level 2 (29,31)].
5. Sucrose and sucrose-containing foods can be substituted for other carbohydrates as part of mixed meals up to a maximum of 10% of total daily energy, provided adequate control of BG and lipids is maintained [Grade B, Level 2 (38,39)].
6. Adults with diabetes should consume no more than 7% of total daily energy from saturated fats [Grade D, Consensus] and should limit intake of trans fatty acids to a minimum [Grade D, Consensus].
7. People with type 1 diabetes should be informed of the risk of delayed hypoglycemia resulting from alcohol consumed with or after the previous evening's meal [Grade C, Level 3 (62)], and should be advised on preventive actions such as carbohydrate intake and/or insulin dose adjustments, and increased BG monitoring [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

- Self-management Education, p. S25
- Physical Activity and Diabetes, p. S37
- Management of Obesity in Diabetes, p. S77
- Complementary and Alternative Medicine in the Management of Diabetes, p. S91
- Dyslipidemia, p. S107
- Treatment of Hypertension, p. S115
- Type 1 Diabetes in Children and Adolescents, p. S150
- Type 2 Diabetes in Children and Adolescents, p. S162
- Diabetes and Pregnancy, p. S168

RELATED WEBSITES

- Canadian Diabetes Association (<http://www.diabetes.ca>)
- Alcohol and Diabetes. Available at: <http://www.diabetes.ca/files/CDAAlcoholFinal.pdf>. Accessed September 1, 2008.

Table 3. Summary of nutritional considerations for people with diabetes**People with diabetes should follow Eating Well with Canada's Food Guide**

- Eat at least 1 dark green and 1 orange vegetable each day; have vegetables and fruit more often than juice
- Make at least half of your grain products whole grain, each day
- Drink lower-fat milk or fortified soy beverages
- Have meat alternatives such as beans, lentils and tofu often
- Eat at least 2 servings of fish each week
- Achieve and maintain a healthy body weight by being active
- Enjoy foods with little or no added fat, sugar or salt
- Satisfy thirst with water

Carbohydrate (45–60% of energy)

- Up to 60 g of added fructose (e.g. fructose-sweetened beverages and foods) in place of an equal amount of sucrose is acceptable
- Intake of <10 g/day of sugar alcohols (maltitol, mannitol, sorbitol, lactitol, isomalt and xylitol) is acceptable
- The use of acesulfame potassium, aspartame, cyclamates, saccharin and sucralose is acceptable
- Include vegetables, fruit, whole grains and milk
- Within the same food category, consume low-glycemic-index foods in place of high-glycemic-index foods
- Increase dietary fibre to 25-50 g/day from a variety of sources, including soluble and cereal fibres
- Sucrose intake of up to 10% of total daily energy is acceptable

Protein (15–20% of energy)

- There is no evidence to suggest that usual recommended protein intake should be modified

Fat (<35% of energy)

- Restrict saturated fats to <7% of total daily energy intake and restrict trans fat intake to a minimum
- Limit polyunsaturated fat to <10% of energy intake
- Consume monounsaturated fats instead of saturated fats more often
- Include foods rich in polyunsaturated omega-3 fatty acids and plant oils

Vitamin and mineral supplements

- Routine supplementation is not necessary, except for vitamin D in persons aged >50 years and folic acid in women who could become pregnant
- In the case of an identified deficiency, limited dietary intake or special need, supplementation may be recommended

Alcohol

- People using insulin or insulin secretagogues should be aware of the risk of delayed hypoglycemia that can occur up to 24 hours after alcohol consumption
- Limit intake to 1–2 drinks per day (≤14 standard drinks per week for men and ≤9 per week for women)

- Basic Carbohydrate Counting for Diabetes Management. Available at: http://www.diabetes.ca/files/Carb_Counting_eng.qx.pdf. Accessed September 1, 2008.
- Cholesterol and Diabetes. Available at: <http://www.diabetes.ca/files/CholesterolToolFINALEng.pdf>. Accessed September 1, 2008.
- Eating Away from Home. Available at: <http://www.diabetes.ca/files/EatingEnglish.pdf>. Accessed September 1, 2008.
- The Glycemic Index. Available at: http://www.diabetes.ca/files/Diabetes_GL_FINAL2_CPG03.pdf. Accessed September 1, 2008.
- Handy Portion Guide. Available at: <http://www.diabetes.ca>. Accessed September 1, 2008.
- Just the Basics – Tips for healthy eating, diabetes prevention and management. Available at: http://www.diabetes.ca/files/JTB17x_11_CPG03_1103.pdf. Accessed September 1, 2008.
- Sugars and Sweeteners. Available at: http://www.diabetes.ca/files/en_sweeteners_final.pdf. Accessed September 1, 2008.

Canadian Diabetes Association, Dietitians of Canada. Nutrition Labelling Education Centre. Available at: <http://www.healthyeatinginstore.ca>. Accessed September 1, 2008.

Health Canada. *Eating Well with Canada's Food Guide*. Available at: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index_e.html. Accessed September 1, 2008.

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Insulin Therapy in Type 1 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Basal-prandial insulin regimens (e.g. multiple daily injections or continuous subcutaneous insulin infusion) are the insulin regimens of choice for all adults with type 1 diabetes.
- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management.
- All individuals with type 1 diabetes should be counselled about the risk, prevention and treatment of insulin-induced hypoglycemia.

INTRODUCTION

Insulin therapy remains the mainstay of glycemic control in people with type 1 diabetes. Insulin preparations are primarily produced by recombinant DNA technology, and are formulated either as structurally identical to human insulin or as a modification of human insulin (insulin analogues) to alter their pharmacokinetics. Animal insulins are becoming less commercially available.

Insulin preparations are classified according to their duration of action, and are further differentiated by their time of onset and peak actions (Table 1). Premixed insulin preparations are available, but are not generally suitable for intensive treatment in patients with type 1 diabetes, who usually need to frequently change the individual components of their insulin regimens.

INSULIN DELIVERY SYSTEMS

Insulin can be administered by syringe, pen or pump (continuous subcutaneous insulin infusion [CSII]). Insulin pen devices facilitate the use of multiple injections of insulin. CSII therapy is a safe and effective method of intensive insulin therapy for selected patients and may provide some advantages over other methods of intensive therapy, particularly in individuals with higher baseline glycated hemoglobin (A1C) (1-5).

INITIATION OF INSULIN THERAPY

Patients must receive initial and ongoing education that includes comprehensive information on how to care for and use insulin; prevention, recognition and treatment of hypoglycemia; sick-day management; adjustments for food intake

(e.g. carbohydrate counting) and physical activity; and self-monitoring of blood glucose (SMBG).

INSULIN REGIMENS

Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management. Social and financial aspects should also be considered. After insulin initiation, some patients go through a "honeymoon period," during which insulin requirements may decrease. This period is, however, transient (usually weeks to months), and insulin requirements will increase with time.

While fixed-dose regimens (conventional therapy) were once the most commonly used regimens and are occasionally still used, they are not preferred. The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive treatment of type 1 diabetes significantly delays the onset and slows the progression of microvascular and macrovascular complications (6,7). The most successful protocols for type 1 diabetes rely on basal-bolus (basal-prandial) regimens that are used as a component of intensive diabetes therapy. Basal insulin is provided by an intermediate-acting insulin or a long-acting insulin analogue once or twice daily. Prandial (bolus) insulin is provided by a short-acting insulin or a rapid-acting insulin analogue given at each meal. Such protocols attempt to duplicate normal pancreatic insulin secretion. Prandial insulin dose must take into account the carbohydrate content and glycemic index of the carbohydrate consumed, exercise around mealtime and the fact that the carbohydrate to insulin ratio may not be the same for each meal (breakfast, lunch and dinner). Prandial insulins can also be used for correction doses to manage hyperglycemia.

Compared with regular insulin, insulin lispro or insulin aspart in combination with adequate basal insulin result in improved postprandial glycemic control and A1C, while minimizing the occurrence of hypoglycemia (8-11). Regular insulin should ideally be administered 30 to 45 minutes prior to a meal. In contrast, insulin aspart and insulin lispro should be administered 0 to 15 minutes before meals. In fact, their rapid onset of action allows for these insulins to be administered up to 15 minutes after a meal. However, preprandial injections achieve better postprandial control and possibly better overall glycemic control (12,13). Insulin aspart has been associated with improved quality of life (14). Insulin

glulisine, another short-acting analogue that has been approved but is not yet commercially available in Canada, has been shown to be equivalent to insulin lispro for glycemic control, with greater A1C reduction when given preprandially as opposed to postprandially (15,16).

When used as a basal insulin in patients with good glycemic control, the long-acting analogues insulin glargine and insulin detemir (with regular insulin or rapid-acting insulin analogues for meals), result in lower fasting plasma glucose (FPG) levels and less nocturnal hypoglycemia compared with once- or twice-daily NPH insulin (8,17-23). Given the potential severe consequences of nocturnal hypoglycemia (discussed below), the avoidance of this complication is of critical clinical importance. When compared with 4-times-daily NPH insulin, insulin glargine was associated with lower A1C and less hypoglycemia (21). Among people with type 1 diabetes, insulin glargine has been shown to have a longer duration of action compared with detemir (24). Insulin detemir has a flatter pharmacodynamic profile than NPH insulin (22). Twice-daily insulin detemir as the basal component of a basal-bolus insulin regimen has been shown

to reduce nocturnal hypoglycemia compared with twice-daily NPH insulin (23,25). There has been a trend towards improved A1C with both insulin glargine and insulin detemir that has reached significance in several studies (25-28). Due to concerns that alterations in the pharmacokinetics may occur, mixing glargine or detemir with other insulins in the same syringe is not recommended by the manufacturers.

In patients using CSII, insulin aspart and lispro have been shown to be superior to regular insulin by improving postprandial glycemic control and reducing hypoglycemia (29-32).

Although human insulins and insulin analogues are used by virtually all adults with type 1 diabetes, animal insulins are still accessible in Canada (see Related Website, page S49).

INHALED INSULIN

Inhaled insulin has been approved for use in Canada, but is not yet commercially available. It has been studied as a rapid-acting insulin administered before meals in a regimen that uses subcutaneous long-acting insulin either once or twice daily. Studies in adults have demonstrated equivalent glycemic control, reduced FPG levels and increased patient satisfaction

Table 1. Types of insulin

Insulin type (trade name)	Onset	Peak	Duration
Prandial (bolus) insulins			
Rapid-acting insulin analogues (clear) <ul style="list-style-type: none"> • Insulin aspart (NovoRapid) • Insulin lispro (Humalog) • Insulin glulisine (Apidra) 	10–15 min 10–15 min 10–15 min	1–1.5 h 1–2 h 1–1.5 h	3–5 h 3.5–4.75 h 3–5 h
Short-acting insulins (clear) <ul style="list-style-type: none"> • Humulin-R • Novolin ge Toronto 	30 min	2–3 h	6.5 h
Inhaled insulin	10–20 min	2 h	6 h
Basal insulins			
Intermediate-acting (cloudy) <ul style="list-style-type: none"> • Humulin-N • Novolin ge NPH 	1–3 h	5–8 h	Up to 18 h
Long-acting basal insulin analogues (clear) <ul style="list-style-type: none"> • Insulin detemir (Levemir) • Insulin glargine (Lantus) 	90 min	Not applicable	Up to 24 h (glargine 24 h, detemir 16–24 h)
Premixed insulins			
Premixed regular insulin – NPH (cloudy) <ul style="list-style-type: none"> • Humulin 30/70 • Novolin ge 30/70, 40/60, 50/50 	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Premixed insulin analogues (cloudy) <ul style="list-style-type: none"> • Biphasic insulin aspart (NovoMix 30) • Insulin lispro/lispro protamine (Humalog Mix25 and Mix50) 			

Note: Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association; Ottawa, Ontario, Canada) and product monographs for detailed information.

compared with subcutaneous short-acting or rapid-acting insulins (33-36). The short-term safety data demonstrate no clinically significant pulmonary dysfunction (33,34,37). It is recommended, however, that inhaled insulin not be used in those with abnormal baseline spirometry (i.e. forced expiratory volume in 1 second [FEV1] <70% predicted) (38).

HYPOGLYCEMIA

Insulin-induced hypoglycemia is a major obstacle for individuals trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. The negative social and emotional impact of hypoglycemia may make patients reluctant to intensify therapy. The diabetes healthcare team should review the patient's experience with hypoglycemia at each visit. This should include an estimate of cause, frequency, symptoms, recognition, severity and treatment.

Intensive vs. conventional insulin therapy

Hypoglycemia is the most common adverse effect of intensive insulin therapy in patients with type 1 diabetes. In the DCCT, 35% of patients in the conventional treatment group and 65% in the intensive group experienced at least 1 episode of severe hypoglycemia (39,40). In a meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally treated and intensively treated patients, respectively (41). Studies have suggested that with adequate self-management education, appropriate glycemic targets, SMBG and professional support, intensive therapy may result in less hypoglycemia than reported in the DCCT (42-45).

Rapid-acting insulin analogues vs. regular insulin

Although there are no differences in the magnitude and temporal pattern of the physiologic, symptomatic and counter-regulatory hormonal responses to hypoglycemia induced by regular human insulin or rapid-acting analogues (46,47), the frequency of hypoglycemic events has been shown to be reduced with rapid-acting insulin analogues compared with regular insulin (8-11).

Long-acting insulin analogues vs. intermediate-acting insulins

Studies have shown reduced incidence of nocturnal hypoglycemia when a long-acting insulin analogue is used in lieu of an intermediate-acting insulin as the basal insulin (48-51). This is an important clinical consideration, as nocturnal hypoglycemia has potential for significant adverse effects.

Lifestyle factors

Deviations from recommended or appropriate self-management behaviours (such as eating less food, taking more insulin,

engaging in more activity) account for 85% of hypoglycemic episodes (52,53). For patients managed with fixed-dose insulin regimens, care should be taken to develop an individualized meal and activity plan that the person can and will follow (54). Adding bedtime snacks may be helpful to avoid nocturnal hypoglycemia among those taking NPH as the basal insulin, or in those individuals at high risk of severe hypoglycemia (regardless of insulin type), particularly when bedtime plasma glucose (PG) levels are <7.0 mmol/L (55,56).

Knowledge of the acute effects of exercise is mandatory. Low- to moderate-intensity exercise lowers blood glucose (BG) levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on BG levels can be modified by altering diet, insulin and the type and timing of exercise. In contrast, high-intensity exercise raises BG levels during and immediately after the event. SMBG before, during and, especially for many hours after exercise is important for establishing response to exercise and guiding the appropriate management of exercise. If ketosis is present (urine ketone level >8.0 mmol/L or blood ketone level >3.0 mmol/L), exercise should not be performed, as metabolic deterioration will occur (57).

Hypoglycemia unawareness and nocturnal hypoglycemia

Asymptomatic hypoglycemia is the presence of a biochemically documented low BG level without any symptoms. Hypoglycemia unawareness occurs when the threshold for the development of autonomic warning symptoms is close to or lower than the threshold for the neuroglycopenic symptoms, such that the first signs of hypoglycemia will often be confusion or loss of consciousness. Severe hypoglycemic reactions are the primary barrier to achieving glycemic targets in people with type 1 diabetes (58). Severe hypoglycemic episodes occur frequently during sleep or in the absence of hypoglycemia awareness that alerts patients to take actions to correct their BG levels (59,60). The sympathoadrenal response to hypoglycemia is reduced during sleep (61). Asymptomatic nocturnal hypoglycemia is common and often lasts >4 hours (59,62-65). Severe hypoglycemia, resulting in seizures, is more likely to occur at night than during the day (66). To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals using intensive insulin therapy should periodically monitor overnight BG levels at a time that corresponds with the peak action time of their overnight insulin.

In people with type 1 diabetes, hypoglycemia was reported to occur at a mean rate of approximately 2 episodes per week. Increasing frequency of hypoglycemia can lead to a decrease in the normal responses to hypoglycemia (67), which, in turn, can lead to decreased awareness of hypoglycemia and defective glucose counterregulation.

Hypoglycemia unawareness and defective glucose counterregulation are potentially reversible. Strict avoidance of hypoglycemia for a period of 2 days to 3 months has been

associated with improvement in the recognition of severe hypoglycemia, in the counterregulatory hormone responses, or both (42,67-73). Structured educational and psychobehavioural programs (e.g. blood glucose awareness training) may help improve detection of hypoglycemia and reduce frequency of severe hypoglycemia (74,75).

RECOMMENDATIONS

Insulin regimens for type 1 diabetes

1. To achieve glycaemic targets in adults with type 1 diabetes, multiple daily insulin injections (prandial [bolus] and basal insulin) or the use of CSII as part of an intensive diabetes management regimen is the treatment of choice [Grade A, Level 1A (6)].
2. Rapid-acting insulin analogues (aspart or lispro), in combination with adequate basal insulin, should be considered over regular insulin to improve A1C while minimizing the occurrence of hypoglycemia [Grade B, Level 2 (9,11)] and to achieve postprandial glucose targets [Grade B, Level 2 (76)].
3. Insulin aspart or insulin lispro should be used when CSII is used in adults with type 1 diabetes [Grade B, Level 2 (29,30)].
4. A long-acting insulin analogue (detemir, glargine) may be considered as an alternative to NPH as the basal insulin [Grade B, Level 2 (17-20)] to reduce the risk of hypoglycemia [Grade B, Level 2 (50), for detemir; Grade C, Level 3 (51), for glargine], including nocturnal hypoglycemia [Grade B, Level 2 (50), for detemir; Grade D, Consensus, for glargine].

Hypoglycemia

5. All individuals with type 1 diabetes should be counselled about the risk and prevention of insulin-induced hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].
6. In individuals with hypoglycemia unawareness, the following strategies should be implemented to reduce the risk of hypoglycemia and to attempt to regain hypoglycemia awareness:
 - Increased frequency of SMBG, including periodic assessment during sleeping hours [Grade D, Consensus].
 - Less stringent glycaemic targets with avoidance of hypoglycemia [Grade C, Level 3 (72,73)].
 - Consideration of a psychobehavioural intervention program (blood glucose awareness training), if available [Grade B, Level 2 (75)].

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29

Monitoring Glycemic Control, p. S32

Pharmacologic Management of Type 2 Diabetes, p. S53

Hypoglycemia, p. S62

In-hospital Management of Diabetes, p. S71

Management of Acute Coronary Syndromes, p. S119

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

Diabetes and Pregnancy, p. S168

Diabetes in the Elderly, p. S181

RELATED WEBSITE

Health Canada information about animal insulin:

http://hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/qa_qr_insulin_02_2006_e.html Accessed September 1, 2008.

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Pharmacologic Management of Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- If glycemic targets are not achieved within 2 to 3 months of lifestyle management, antihyperglycemic pharmacotherapy should be initiated.
- Timely adjustments to and/or additions of antihyperglycemic agents should be made to attain target A1C within 6 to 12 months.
- In patients with marked hyperglycemia (A1C $\geq 9.0\%$), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to either initiating combination therapy with 2 agents or initiating insulin.

INTRODUCTION

As people with type 2 diabetes form a heterogeneous group, treatment regimens and therapeutic targets should be individualized. Blood glucose (BG) levels close to the normal range should be the goal for individuals in whom it is deemed safe. As type 2 diabetes is characterized by insulin resistance and ongoing decline in beta cell function, glucose levels will likely worsen over time (1) and treatment must be dynamic. The number of available antihyperglycemic agents is expanding, requiring the clinician to consider many of the following factors when choosing medications: degree of hyperglycemia, risk of hypoglycemia, medication side effects, concomitant medical conditions, ability to adhere to regimen and patient preferences. Lifestyle modification, including nutritional therapy and physical activity, should continue to be emphasized while pharmacotherapy is being used.

TREATMENT REGIMENS

The diagnosis of type 2 diabetes is often delayed, and 20 to 50% of people with type 2 diabetes present with microvascular and/or macrovascular complications at the time of diagnosis (2,3). When lifestyle interventions fail to control BG levels adequately, pharmacologic treatment becomes necessary.

In the face of more severe hyperglycemia (i.e. glycated hemoglobin [A1C] $\geq 9.0\%$), combinations of agents are usually required. The lag period before adding other antihyperglycemic agent(s) should be kept to a minimum, taking into account the characteristics of the different medications. With timely adjustments to and/or additions of antihyperglycemic agents, the target A1C level should be attainable within 6 to 12 months.

In general, A1C will decrease by about 0.5 to 1.5% with monotherapy, depending on the agent used and the baseline A1C level (4). Generally, the higher the baseline A1C, the greater the A1C reduction for each given agent. In general, as A1C levels decrease toward normal levels ($<7.3\%$), postprandial BG control assumes greater importance for further A1C reduction (5).

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses (6-9). Furthermore, many patients on monotherapy with the late addition of another antihyperglycemic agent may not readily attain target BG levels (1). When combining antihyperglycemic agents with or without insulin, classes of agents that have different mechanisms of action should be used. Simultaneous use of agents from different classes but with similar mechanisms of action (e.g. sulfonylureas and meglitinides; and DPP-4 inhibitors) is currently untested and may be less effective at improving glycemia and is not recommended at this time.

There is debate over which antihyperglycemic agent (including insulin) should be used initially and which agents should be added subsequently. There is also debate over which agents within a given class might be preferred in specific situations. Symptomatic patients with high BG and A1C levels require agents that lower BG levels quickly (e.g. insulin). However, the issue of how to reach glycemic targets may be less important than the need to achieve that target. Improved BG and A1C levels are associated with better outcomes, even if recommended glycemic targets cannot be reached (3). Each of the agents listed in Table 1 (10-51) and Figure 1 has advantages and disadvantages (e.g. degree of BG lowering, risk of hypoglycemia and nonglycemic benefits/risks).

The recommendation to use metformin as the initial agent in most patients is based on its effectiveness in lowering BG, its relatively mild side effect profile and its demonstrated benefit in overweight patients (52). While monotherapy with an insulin sensitizer (thiazolidinedione [TZD]) produces more long-lasting glycemic control compared to metformin or sulfonylurea therapy (45), the edema, weight gain, small risk of congestive heart failure (CHF), increased risk of fractures in women (44,46) and inconsistent data regarding cardiovascular outcomes (53) offset the potential for this class to be recommended as first-line therapy. Although meta-analyses of

Table 1. Antihyperglycemic agents for use in type 2 diabetes

Class*	Drug (brand name)	Expected decrease in A1C with monotherapy	Hypoglycemia	Other therapeutic considerations
Alpha-glucosidase inhibitor	acarbose (Glucobay) (10-12)	↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥9.0%) • Often used in combination with other oral antihyperglycemic agents • Weight neutral as monotherapy • GI side effects
Incretin agent (13-15)	DPP-4 inhibitor sitagliptin (Januvia)	↓ to ↓↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • Weight neutral • Improved postprandial control • Newer agent with unknown long-term safety
Insulin (3,16-22)	Rapid-acting analogues aspart (NovoRapid) glulisine (Apidra) lispro (Humalog) Short-acting regular (Humulin-R, Novolin ge Toronto) Intermediate-acting NPH (Humulin-N, Novolin ge NPH) Long-acting basal analogues detemir (Levemir) glargine (Lantus) Premixed Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) Biphasic insulin aspart (NovoMix 30) Insulin lispro/lispro protamine (Humalog Mix25, Mix50)	Depends on regimen, but up to ↓↓	Significant risk	<ul style="list-style-type: none"> • Potentially greatest A1C reduction and no maximal dose • Numerous formulations and delivery systems (including subcutaneous-injectable) allow for regimen flexibility • Hypoglycemia risk highest with regular and NPH insulin • When initiating insulin, consider adding bedtime intermediate-acting insulin or long-acting insulin analogue to daytime oral antihyperglycemic agents (although other regimens can be used) • Intensive insulin therapy regimen recommended if above fails to attain glycemic targets • Increased risk of weight gain relative to sulfonylureas and metformin
Insulin secretagogues	Sulfonylureas gliclazide (Diamicon, Diamicon MR, generic) (23,24)	↓ ↓	Minimal/moderate risk	<ul style="list-style-type: none"> • Relatively rapid BG-lowering response • All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective) • Postprandial glycemia is especially reduced by nateglinide and repaglinide • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure) • If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia (32) and glimepiride is associated with less hypoglycemia than glyburide (27) • Nateglinide and repaglinide are associated with less hypoglycemia in the context of missed meals
	glimepiride (Amaryl) (25-27)	↓ ↓	Moderate risk	
	glyburide (Diabeta, Euglucon, generic) (3) (note: chlorpropamide and tolbutamide are still available in Canada, but rarely used)	↓ ↓	Significant risk	
	Meglitinides nateglinide (Starlix) (28) repaglinide (GlucNorm) (29-31)	↓ ↓	Minimal/moderate risk Minimal/moderate risk	

Metformin	Glucophage, Glumetza, generic (33,34)	↕↕	Negligible risk as monotherapy	<ul style="list-style-type: none"> Improved cardiovascular outcomes in overweight subjects Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure Caution if CrCl/eGFR <60 mL/min Weight neutral as monotherapy, promotes less weight gain when combined with other antihyperglycemic agents, including insulin GI side effects
TZDs (35-45)	pioglitazone (Actos) rosiglitazone (Avandia)	↕↕	Negligible risk as monotherapy	<ul style="list-style-type: none"> Longer duration of glycemic control with monotherapy compared to metformin or glyburide Mild BP lowering Between 6 and 12 weeks required to achieve full glycemic effect Weight gain (waist-to-hip ratio not increased) May induce edema and/or heart failure Avoid in patients with heart failure Higher rates heart failure when combined with insulin[†] Rare occurrence of macular edema Rare occurrence of fractures in females (44,46) Suggestion of increased risk of cardiovascular events with rosiglitazone awaits further study
Antiobesity agents	orlistat (Xenical) (47-49)	↘	None	<ul style="list-style-type: none"> Promote weight loss
	sibutramine (Meridia) (50,51)	↘	None	<ul style="list-style-type: none"> Glycemic benefit may be limited to those who actually lose weight Orlistat can cause diarrhea and other GI side effects Sibutramine can increase heart rate and BP
Combined formulations	Avandamet (metformin + rosiglitazone)	↕↕↕	Negligible risk as monotherapy	See metformin, TZDs, and sulfonyleureas
	Avandaryl (glimepiride + rosiglitazone)	↕↕↕	Moderate risk	

*Listed in alphabetical order

[†]Combining insulin with a TZD is not an approved indication in Canada

↘: <1.0% reduction in A1C

↕↕: 1.0–2.0% reduction in A1C

↕↕↕: >2.0% reduction in A1C

A1C = glycated hemoglobin

BG = blood glucose

BP = blood pressure

CrCl = creatinine clearance

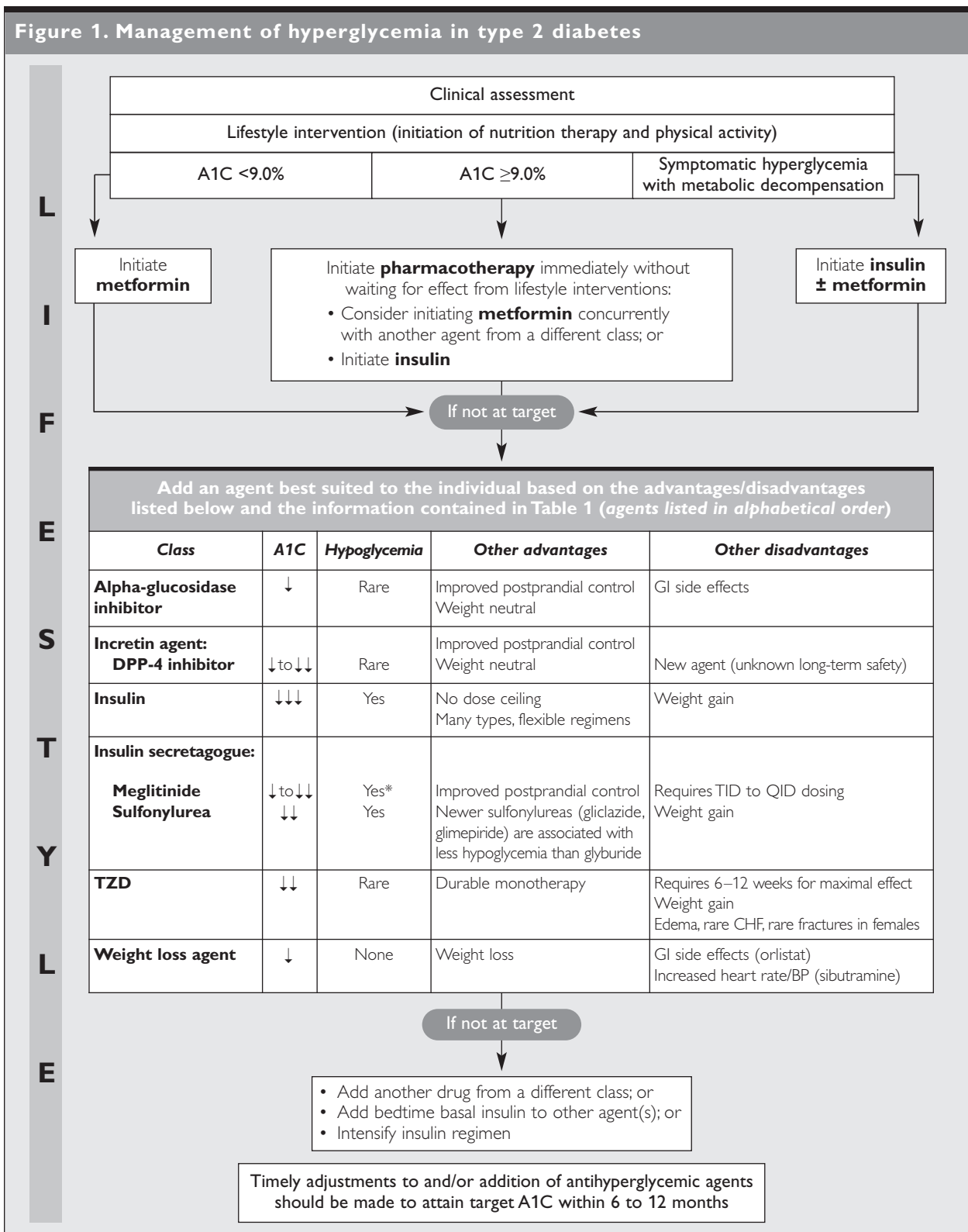
eGFR = estimated glomerular filtration rate

GI = gastrointestinal

TZD = thiazolidinedione

Note: Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and detailed prescribing information.

Figure 1. Management of hyperglycemia in type 2 diabetes



A1C = glycated hemoglobin

BP = blood pressure

CHF = congestive heart failure

DPP-4 = dipeptidyl peptidase-4

GI = gastrointestinal

TZD = thiazolidinedione

↓ = <1.0% decrease in A1C

↓↓ = 1.0–2.0% decrease in A1C

↓↓↓ = >2.0% decrease in A1C

Note: Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information

*Less hypoglycemia in the context of missed meals

smaller underpowered studies suggested possible cardiovascular harm specific to TZD use (54,55) this has not been demonstrated in larger randomized clinical trials (56-58).

In patients for whom hypoglycemia is a particular concern, agents associated with less hypoglycemia are preferred. Table 1 and Figure 1 provide information to aid decision-making.

A combination of oral antihyperglycemic agents and insulin often effectively controls glucose levels. When insulin is added to oral antihyperglycemic agent(s), a single injection of intermediate-acting (NPH) (6,59), or an extended long-acting insulin analogue (insulin glargine or insulin detemir) (19) may be added. This approach may result in better glycemic control with a smaller dose of insulin (60) and may induce less weight gain and less hypoglycemia than that seen when oral agents are stopped and insulin is used alone (33). The addition of bedtime insulin to metformin therapy leads to less weight gain than insulin plus a sulfonyleurea or twice-daily NPH insulin (16). While combining insulin with a TZD is not an approved indication in Canada, the addition of such agents to insulin in carefully selected patients improves glycemic control and reduces insulin requirements (61). Such combination can result in increased weight, fluid retention and, in few patients, CHF. Inhaled insulin (approved, but not yet available in Canada) can also be added to oral antihyperglycemic therapy to help control BG levels, but can cause

cough and slight reductions in pulmonary function tests (62). The use of inhaled insulin should be restricted to non-smokers and those without respiratory disorders. Pulmonary function tests should be done at baseline, 6 months and annually during inhaled insulin therapy.

Insulin can be used at diagnosis in individuals with marked hyperglycemia and can be used temporarily during illness, pregnancy, stress, or for a medical procedure or surgery. There is no evidence that exogenous insulin accelerates the risk of macrovascular complications of diabetes, and its appropriate use should be encouraged (63). When insulin is used in type 2 diabetes, the insulin regimen should be tailored to achieve good metabolic control while trying to avoid severe hypoglycemia. With intensive glycemic control, there is an increased risk of hypoglycemia, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. The number of insulin injections (1-4 per day) and the timing of injections may vary depending on each individual's situation (64). The reduction in A1C achieved with insulin therapy depends on the dose and number of injections per day of insulin.

As type 2 diabetes progresses, insulin doses will likely need to be increased, additional doses of basal insulin (intermediate-acting or long-acting analogues) may need to be added, and prandial insulin (short-acting or rapid-acting analogues or inhaled insulin) may also be required.

RECOMMENDATIONS

1. In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agents should be initiated [Grade A, Level 1A (3)]. In the presence of marked hyperglycemia (A1C $\geq 9.0\%$), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents or initiating insulin treatment in symptomatic individuals [Grade D, Consensus].
2. If glycemic targets are not attained when a single antihyperglycemic agent is used initially, an antihyperglycemic agent or agents from different classes should be added. The lag period before adding other agent(s) should be kept to a minimum, taking into account the characteristics of the different agents. Timely adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C within 6 to 12 months [Grade D, Consensus].
3. Pharmacological treatment regimens should be individualized taking into consideration the degree of hyperglycemia and the properties of the antihyperglycemic agents including: effectiveness in lowering BG, durability of glycemic control, side effects, contraindications, risk of hypoglycemia, presence of diabetes complications or comorbidities, and patient preferences [Grade D, Consensus]. The following factors and the information shown in Table 1 and Figure 1 should also be taken into account:
 - Metformin should be the initial drug used in both overweight patients [Grade A, Level 1A (52)] and nonoverweight patients [Grade D, Consensus].
 - Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and Table 1 [Grade D, Consensus].
4. When basal insulin is added to antihyperglycemic agents, long-acting analogues (insulin detemir or insulin glargine) may be considered instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (71)].
5. The following antihyperglycemic agents (listed in alphabetical order), should be considered to lower postprandial BG levels:
 - Alpha-glucosidase inhibitor [Grade B, Level 2 (10)]
 - Premixed insulin analogues (i.e. biphasic insulin aspart and insulin lispro/protamine) instead of regular/ NPH premixtures [Grade B, Level 2 (72,73)]
 - DPP-4 inhibitor [Grade A, Level 1 (13,14,74)]
 - Inhaled insulin [Grade B, Level 2 (20)].
 - Meglitinides (repaglinide, nateglinide) instead of sulfonyleureas [Grade B, Level 2 (75,76)]
 - Rapid-acting insulin analogues (aspart, glulisine, lispro) instead of short-acting insulin (i.e. regular insulin) [Grade B, Level 2 (21,77,78)].
6. All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the recognition and prevention of drug-induced hypoglycemia [Grade D, Consensus].

HYPOGLYCEMIA

Medication-induced hypoglycemia is the most common cause of hypoglycemia. It is estimated that hypoglycemia of any severity occurs annually in up to approximately 20% of patients taking insulin secretagogues (65). Although these hypoglycemic episodes are rarely fatal, they can be associated with serious clinical sequelae. Therefore, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin secretagogues. Few large, randomized clinical trials have compared the rates of hypoglycemia between these agents.

In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of adults with type 2 diabetes who experienced a severe hypoglycemic episode per year was significantly higher in the intensive group than in the conventional group (3), particularly for patients using insulin therapy. Although the risk of hypoglycemia was less than that seen in the patients with type 1 diabetes in the Diabetes Control and Complications Trial, each year approximately 3% of patients treated with insulin in the UKPDS experienced a severe hypoglycemic episode, and 40% had a hypoglycemic episode of any severity (3).

Lower rates of hypoglycemia have been observed in some studies of patients with type 2 diabetes treated with rapid-acting insulin analogues (insulin aspart, insulin lispro, insulin glulisine) compared to those treated with short-acting (regular) insulin (66,67). Use of long-acting basal insulin analogues (insulin detemir, insulin glargine) reduces the risk of nocturnal hypoglycemia compared to treatment with NPH insulin (19,68-70).

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29

Insulin Therapy in Type 1 Diabetes, p. S46

Hypoglycemia, p. S62

Management of Obesity in Diabetes, p. S77

Type 2 Diabetes in Children and Adolescents, p. S162

Diabetes and Pregnancy, p. S168

Diabetes in the Elderly, p. S181

RELEVANT APPENDIX

Appendix 3: Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

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Hypoglycemia

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Jean-François Yale MD CSPQ

KEY MESSAGES

- It is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues.
- The goals of treatment for hypoglycemia are to detect and treat a low blood glucose (BG) level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly.
- It is important to avoid overtreatment, since this can result in rebound hyperglycemia and weight gain.

INTRODUCTION

Drug-induced hypoglycemia is a major obstacle for individuals (especially those with type 1 diabetes) trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. The negative social and emotional impact of hypoglycemia may make patients reluctant to intensify therapy. As such, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues. (See “Insulin Therapy in Type 1 Diabetes,” p. S46, and “Pharmacologic Management of Type 2 Diabetes,” p. S53, for further discussion of drug-induced hypoglycemia.)

DEFINITION OF HYPOGLYCEMIA

Hypoglycemia is defined by: 1) the development of autonomic or neuroglycopenic symptoms (Table 1); 2) a low plasma glucose (PG) level (<4.0 mmol/L for patients treated with insulin or an insulin secretagogue); and 3) symptoms responding to the administration of carbohydrate (1). The severity of hypoglycemia is defined by clinical manifestations (Table 2).

COMPLICATIONS OF SEVERE HYPOGLYCEMIA

Short-term risks of hypoglycemia include the dangerous situations that can arise while an individual is hypoglycemic, whether at home or work (e.g. driving, operating machinery). In addition, prolonged coma is sometimes associated

with transient neurological symptoms such as paresis, convulsions and encephalopathy. The potential long-term complications of severe hypoglycemia are mild intellectual impairment and permanent neurologic sequelae such as hemiparesis and pontine dysfunction. The latter are rare and have been reported only in case studies.

Retrospective studies have suggested a link between frequent severe hypoglycemia (≥ 5 episodes since diagnosis) and a decrease in intellectual performance. These changes were small but, depending on an individual's occupation, could be clinically meaningful. In contrast, prospective studies have not found an association between intensive insulin therapy and cognitive function (2,3). A meta-analysis concluded that lowered cognitive performance in people with diabetes appeared to be associated with the presence of microvascular complications, but not with the occurrence of severe hypoglycemic episodes or with poor metabolic control (4).

The major risk factors for severe hypoglycemia in patients with type 1 diabetes include prior episode of severe hypoglycemia (5-7), current low glycated hemoglobin (A1C) ($<6.0\%$) (6,8-10), hypoglycemia unawareness (11),

Table 1. Symptoms of hypoglycemia

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
Tingling	Headache
	Dizziness

Table 2. Severity of hypoglycemia

Mild: Autonomic symptoms are present. The individual is able to self-treat.
Moderate: Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.
Severe: Individual requires assistance of another person. Unconsciousness may occur. PG is typically <2.8 mmol/L.

PG = plasma glucose

long duration of diabetes (9,12), autonomic neuropathy (13), adolescence (14) and preschool-age children unable to detect and/or treat mild hypoglycemia on their own. Patients at high risk for severe hypoglycemia should be informed of their risk and counselled, along with their significant others, on preventing and treating hypoglycemia (including use of glucagon), preventing driving and industrial accidents through self-blood glucose monitoring and taking appropriate precautions prior to the activity, and documenting blood glucose (BG) readings taken during sleeping hours. Individuals may need to have their insulin regimen adjusted appropriately to lower their risk. Risk factors for severe hypoglycemia are shown in Table 3.

TREATMENT OF HYPOGLYCEMIA

The goals of treatment for hypoglycemia are to detect and treat a low BG level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. It is also important to avoid overtreatment, since this can result in rebound hyperglycemia and weight gain.

Evidence suggests that 15 g of glucose (monosaccharide) is required to produce an increase in BG of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people (Table 4) (15-19). This has not been well studied in patients with gastropathy. A 20-g oral glucose dose will produce a BG increment of approximately 3.6 mmol/L at 45 minutes (16,17). Other choices such as milk and orange juice are slower to increase BG levels and provide symptom relief (16,17). Glucose gel is quite slow (<1.0 mmol/L increase at 20 minutes) and must be swallowed to have a significant effect (15,20). Patients taking an alpha-glucosidase inhibitor (acarbose) must use glucose (dextrose) tablets (21) or, if unavailable, milk or honey to treat hypoglycemia. Glucagon 1 mg subcutaneously or intramuscularly produces a significant increase in BG (from 3.0 mmol/L to 12.0 mmol/L) within 60 minutes (22). The effect is impaired in individuals whom have consumed more than 2 standard alcoholic drinks in the previous few hours, or in those who have advanced liver disease (23).

Table 3. Risk factors for severe hypoglycemia in patients with type 1 diabetes

- Prior episode of severe hypoglycemia
- Current low A1C (<6.0%)
- Hypoglycemia unawareness
- Long duration of diabetes
- Autonomic neuropathy
- Low economic status
- Adolescence
- Preschool-age children unable to detect and/or treat mild hypoglycemia on their own

A1C = glycated hemoglobin

Table 4. Examples of 15 g of carbohydrate for the treatment of mild to moderate hypoglycemia

- 15 g of glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water
- 175 mL (3/4 cup) of juice or regular soft drink
- 6 Life Savers (1=2.5 g of carbohydrate)
- 15 mL (1 tablespoon) of honey

RECOMMENDATIONS

1. Mild to moderate hypoglycemia should be treated by the oral ingestion of 15 g of carbohydrate, preferably as glucose or sucrose tablets or solution. These are preferable to orange juice and glucose gels [Grade B, Level 2 (15)]. Patients should be encouraged to wait 15 minutes, retest BG and retreat with another 15 g of carbohydrate if the BG level remains <4.0 mmol/L [Grade D, Consensus].
2. Severe hypoglycemia in a conscious person should be treated by the oral ingestion of 20 g of carbohydrate, preferably as glucose tablets or equivalent. Patients should be encouraged to wait 15 minutes, retest BG and retreat with another 15 g of glucose if the BG level remains <4.0 mmol/L [Grade D, Consensus].
3. Severe hypoglycemia in an unconscious individual >5 years of age, in the home situation, should be treated with 1 mg of glucagon subcutaneously or intramuscularly. Caregivers or support persons should call for emergency services and the episode should be discussed with the diabetes healthcare team as soon as possible [Grade D, Consensus].
4. For individuals at risk of severe hypoglycemia, support persons should be taught how to administer glucagon by injection [Grade D, Consensus].
5. To treat severe hypoglycemia with unconsciousness, when intravenous access is available, glucose 10 to 25 g (20 to 50 cc of D50W) should be given over 1 to 3 minutes [Grade D, Consensus].
6. To prevent repeated hypoglycemia, once the hypoglycemia has been reversed, the person should have the usual meal or snack that is due at that time of the day. If a meal is >1 hour away, a snack (including 15 g of carbohydrate and a protein source) should be consumed [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29
 Monitoring Glycemic Control, p. S32
 Insulin Therapy in Type 1 Diabetes, p. S46
 Pharmacologic Management of Type 2 Diabetes, p. S53
 Type 1 Diabetes in Children and Adolescents, p. S150
 Diabetes and Pregnancy, p. S168
 Diabetes in the Elderly, p. S181

RELATED WEBSITE

Begg IS, Yale J-F, Houlden RL, et al. Canadian Diabetes Association's clinical practice guidelines for diabetes and private and commercial driving. *Can J Diabetes*. 2003;27:128-140. Available at: <http://www.diabetes.ca/files/DrivingGuidelinesBeggJune03.pdf>. Accessed September 1, 2008.

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Hyperglycemic Emergencies in Adults

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) should be suspected in ill patients with diabetes. If either DKA or HHS is diagnosed, precipitating factors must be sought and treated.
- DKA and HHS are medical emergencies that require treatment and monitoring for multiple metabolic abnormalities and vigilance for complications.
- Ketoacidosis requires insulin administration (0.1 U/kg/hour) for resolution; bicarbonate therapy should be considered only for extreme acidosis ($\text{pH} \leq 7.0$).

Note to readers: Although the diagnosis and treatment of diabetic ketoacidosis (DKA) in adults and in children share general principles, there are significant differences in their application, largely related to the increased risk of life-threatening cerebral edema with DKA in children and adolescents. The specific issues related to treatment of DKA in children and adolescents are addressed in "Type 1 Diabetes in Children and Adolescents," p. S150.

INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are diabetes emergencies with overlapping features. With insulin deficiency, hyperglycemia causes urinary losses of water and electrolytes (sodium, potassium, chloride) and the resultant extracellular fluid volume (ECFV) depletion. Potassium is shifted out of cells, and ketoacidosis occurs as a result of elevated glucagon levels and absolute insulin deficiency (in the case of type 1 diabetes) or high catecholamine levels suppressing insulin release (in the case of type 2 diabetes). In DKA, ketoacidosis is prominent, while in HHS the main features are ECFV depletion and hyperosmolality.

Risk factors for DKA include new diagnosis of diabetes mellitus, insulin omission, infection, myocardial infarction, abdominal crisis, trauma and possibly treatment with insulin infusion pumps.

HHS is much less common than DKA (1,2). In addition to the precipitating factors noted above for DKA, HHS has also been reported following cardiac surgery, and with the use of certain drugs, including diuretics, glucocorticoids, lithium and atypical antipsychotics.

The clinical presentation of DKA includes symptoms of hyperglycemia, Kussmaul respiration, acetone-odoured breath, ECFV contraction, nausea, vomiting and abdominal pain. There may be a decreased level of consciousness. In HHS, there is often more profound ECFV contraction and decreased level of consciousness (proportional to the elevation in plasma osmolality). In addition, in HHS there can be a variety of neurological presentations, including seizures and a stroke-like state that can resolve once osmolality returns to normal (2-4). In both conditions, there may also be evidence of a precipitating condition.

DIAGNOSIS

DKA or HHS should be suspected whenever patients have significant hyperglycemia, especially if they are ill or highly symptomatic (see above). As outlined in Figure 1, to make the diagnosis and determine the severity of DKA or HHS, the following should be assessed: plasma levels of electrolytes (and anion gap), glucose, creatinine, osmolality and beta-hydroxybutyric acid (beta-OHB) (if available), blood gases, serum and urine ketones, fluid balance, level of consciousness, precipitating factors and complications (5).

There are no definitive criteria for the diagnosis of DKA. Typically, the arterial pH is ≤ 7.3 , serum bicarbonate is ≤ 15 mmol/L, and the anion gap is >12 mmol/L with positive serum and/or urine ketones (5-7). Plasma glucose is usually ≥ 14.0 mmol/L, but can be lower (8). DKA is more challenging to diagnose in the presence of the following conditions: 1) mixed acid-base disorders (such as associated vomiting, which will raise the bicarbonate level); 2) if there has been a shift in the redox potential favouring the presence of beta-OHB (rendering serum ketone testing negative); or 3) if the loss of ketoanions with sodium or potassium in osmotic diuresis has occurred, leading to a return of the plasma anion gap towards normal. It is therefore important to measure ketones in both the serum and urine. If there is an elevated anion gap, and serum ketones are negative, beta-OHB levels should be measured. Measurement of serum lactate should be considered in hypoxic states. In HHS, a more prolonged duration of relative insulin insufficiency and inadequate fluid intake (or high glucose intake) results in higher glucose levels (typically ≥ 34.0 mmol/L) and greater ECFV contraction, but minimal acid-base disturbance (5,6).

MANAGEMENT

Objectives of management include restoration of normal ECFV and tissue perfusion; resolution of ketoacidosis; correction of electrolyte imbalances and hyperglycemia; and the diagnosis and treatment of coexistent illness. The issues that must be addressed in the patient presenting with DKA or HHS are outlined in Table 1. A summary of fluid therapy is outlined in Table 2, and a management algorithm and formulas for calculating key measurements are provided in Figure 1.

Table 1. Priorities* to be addressed in the management of patients presenting with hyperglycemic emergencies

Metabolic	Precipitating cause of DKA/HHS	Other complications of DKA/HHS
<ul style="list-style-type: none"> •ECFV contraction •Potassium deficit and abnormal concentration •Metabolic acidosis •Hyperosmolality (water deficit leading to increased corrected sodium concentration plus hyperglycemia) 	<ul style="list-style-type: none"> •New diagnosis of diabetes •Insulin omission •Infection •Myocardial infarction •Drugs 	<ul style="list-style-type: none"> •Hyper/hypokalemia •ECFV overexpansion •Cerebral edema •Hypoglycemia •Pulmonary emboli •Aspiration •Hypocalcemia (if phosphate used) •Stroke •Acute renal failure •Deep vein thrombosis

*Severity of issue will dictate priority of action

DKA = diabetic ketoacidosis

ECFV = extracellular fluid volume

HHS = hyperosmolar hyperglycemic state

Table 2. Summary of fluid therapy for DKA and HHS in adults

1. Administer IV normal saline initially. If the patient is in shock, give 1 to 2 L/hour initially to correct shock; otherwise, give 500 mL/hour for 4 hours, then 250 mL/hour for 4 hours.
2. Add potassium immediately if patient is normo- or hypokalemic. Otherwise, if initially hyperkalemic, only add potassium once serum potassium falls to <5 to 5.5 mmol/L and patient is diuresing.
3. Once plasma glucose reaches 14.0 mmol/L, add glucose to maintain plasma glucose at 12.0 to 14.0 mmol/L.
4. After hypotension has been corrected, switch normal saline to half-normal saline (with potassium chloride). However, if plasma osmolality is falling more rapidly than 3 mmol/kg/hour and/or the corrected plasma sodium is reduced, maintain IV fluids at higher osmolality (i.e. may need to maintain on normal saline).

DKA = diabetic ketoacidosis

HHS = hyperosmolar hyperglycemic state

IV = intravenous

Patients with DKA and HHS are best managed in an intensive care unit (ICU) or step-down setting (5-7) with specialist care (9,10). Volume status (including fluid intake and output), vital signs, neurologic status, plasma concentrations of electrolytes, anion gap, osmolality and glucose need to be monitored closely, initially as often as every 2 hours (5-7). Precipitating factors must be diagnosed and treated (5-7).

ECFV contraction

The sodium deficit is typically 7.0 to 10.0 mmol/kg in DKA (11) and 5 to 13 mmol/kg in HHS (12), which along with water losses (100 mL/kg and 100–200 mL/kg, respectively) (11,12) results in decreased ECFV, usually with decreased intracellular fluid volume. Restoring ECFV improves tissue perfusion and reduces plasma glucose levels by both dilution and by increasing urinary glucose losses. ECFV re-expansion using a rapid rate of initial fluid administration was associated with an increased risk of cerebral edema (CE) in 1 study (13) but not in another (14). In adults, one should initially administer intravenous (IV) normal saline 1 to 2 L/hour to correct shock, otherwise 500 mL/hour for 4 hours, then 250 mL/hour of IV fluids (15,16).

Potassium deficit

The typical potassium deficit range is 2 to 5 mmol/kg in DKA and 4 to 6 mmol/kg in HHS (12,13). There have been no randomized trials that have studied strategies for potassium replacement. Typical recommendations suggest that potassium supplementation should be started for plasma potassium <5.0 to 5.5 mmol/L once diuresis has been established, usually with the second litre of saline. If the patient at presentation is normo- or hypokalemic, potassium should be given immediately, at concentrations in the IV fluid between 10 and 40 mmol/L, at a maximum rate of 40 mmol/hour. In the case of frank hypokalemia (potassium <3.3 mmol/L), insulin should be withheld until potassium replacement at 40 mmol/hour has restored plasma potassium to ≥ 3.3 mmol/L (5,6). It is reasonable to treat the potassium deficit of HHS in the same way.

Metabolic acidosis

Metabolic acidosis is a prominent component of DKA. Patients with HHS have minimal or no acidosis. Insulin is used to stop ketoacid production; IV fluid alone has no impact on parameters of ketoacidosis (17). Short-acting insulin (0.1 U/kg/h) is recommended (18-20). Although the use of an initial bolus of IV insulin is recommended in some reviews (5), the effectiveness of this step has not been studied in adults. In children, using an initial bolus of IV insulin does not result in faster resolution of ketoacidosis (21,22). The use of subcutaneous boluses of rapid-acting insulin analogues at 1- to 2-hour intervals results in similar duration of ketoacidosis with no more frequent occurrence of hypoglycemia compared to short-acting IV insulin 0.1 U/kg/hour (23-25). The

dose of insulin should subsequently be adjusted based on ongoing acidosis (26), using the plasma anion gap or beta-OHB measurements. Plasma glucose levels will fall due to multiple mechanisms, including ECFV re-expansion (27), glucose losses via osmotic diuresis (17) and insulin-mediated reduced glucose production and increased cellular uptake of glucose. Once plasma glucose reaches 14.0 mmol/L, IV glucose should be started to avoid hypoglycemia, targeting a plasma glucose of 12.0 to 14.0 mmol/L.

Similar doses of IV insulin can be used to treat HHS, although subjects are not acidemic and the fall in plasma glucose concentration is predominantly due to re-expansion of ECFV and osmotic diuresis (27). Insulin has been withheld successfully in HHS (28), but generally its use is recommended to reduce plasma glucose levels (5,6).

Use of IV sodium bicarbonate to treat acidosis did not affect outcome in randomized controlled trials (29-31). Sodium bicarbonate therapy can be considered in adult patients in shock or with arterial pH ≤ 7.0 . For example, one can administer 1 ampoule (50 mmol) of sodium bicarbonate added to 200 mL of D5W (or sterile water, if available) over 1 hour, repeated every 1 to 2 hours until pH is ≥ 7.0 (5,6). Potential risks associated with the use of sodium bicarbonate include hypokalemia (32) and delayed occurrence of metabolic alkalosis.

Hyperosmolality

Hyperosmolality is due to hyperglycemia and a water deficit. However, serum sodium concentration may be reduced due to shift of water out of cells. The concentration of sodium needs to be corrected for the level of glycemia to determine if there is also a water deficit (see Figure 1). In patients with DKA, plasma osmolality is usually ≤ 320 mmol/kg. In HHS, plasma osmolality is typically > 320 mmol/kg. Because of the risk of CE with rapid reductions in osmolality (33), it has been recommended that the plasma osmolality be lowered no faster than 3 mmol/kg/hour (5,6). This can be achieved by monitoring plasma osmolality, by adding glucose to the infusions when plasma glucose reaches 14.0 mmol/L to maintain it at that level, and selecting the correct concentration of IV saline. Typically, after volume re-expansion, IV fluid is switched to half-normal saline because urinary losses of electrolytes in the setting of osmotic diuresis are usually hypotonic. The potassium in the infusion will also add to the osmolality. If osmolality falls too rapidly despite the administration of glucose, consideration should be given to increasing the sodium concentration of the infusing solution (5,6). Water imbalances can also be monitored using the corrected plasma sodium.

Phosphate deficiency

There is currently no evidence to support the use of phosphate therapy for DKA (34-36), and there is no evidence that hypophosphatemia causes rhabdomyolysis in DKA (37).

However, because hypophosphatemia has been associated with rhabdomyolysis in other states, administration of potassium phosphate in cases of severe hypophosphatemia could be considered for the purpose of trying to prevent rhabdomyolysis.

COMPLICATIONS

In Ontario, in-hospital mortality in patients hospitalized for acute hyperglycemia ranged from $< 1\%$ at ages 20 to 49 years old to 16% in those over age 75 (38). Reported mortality in DKA ranges from 0.65 to 3.3% (2,9,39-41). In HHS, recent studies found mortality rates to be 12 to 17%, but included patients with mixed DKA and hyperosmolality (1,3,42). About 50% of deaths occur in the first 48 to 72 hours. Mortality is usually due to the precipitating cause, to electrolyte imbalances (especially hypo- and hyperkalemia) and to CE.

RECOMMENDATIONS

1. In patients with DKA, a protocol incorporating the principles illustrated in Figure 1 should be followed [Grade D, Consensus]. For HHS, a similar protocol can be used; however, in this case, the plasma glucose level is used to titrate the insulin dose [Grade D, Consensus].
2. In individuals with DKA, IV 0.9% sodium chloride should be administered initially at 500 mL/hour for 4 hours, then 250 mL/hour for 4 hours [Grade B, Level 2 (15)] with consideration of a higher initial rate (1–2 L/hour) in the presence of shock [Grade D, Consensus]. For persons with a HHS, IV fluid administration should be individualized based on the patient's needs [Grade D, Consensus].
3. In patients with DKA, IV short-acting insulin should be administered at an initial dose of 0.1 U/kg/hour [Grade B, Level 2 (19,20)]. The insulin infusion rate should be maintained until the resolution of ketosis [Grade B, Level 2 (24)] as measured by the normalization of the plasma anion gap [Grade D, Consensus]. Once the plasma glucose concentration reaches 14.0 mmol/L, IV dextrose should be started to avoid hypoglycemia [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Type 1 Diabetes in Children and Adolescents, p. S150

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In-hospital Management of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes increases the risk for disorders that predispose individuals to hospitalization, including cardiovascular diseases, nephropathy, infection and lower-extremity amputations.
- Use of “sliding scale” insulin therapy, although common, treats hyperglycemia after it has occurred. A proactive approach to management with the use of basal, bolus and correction insulin is preferred.
- Hypoglycemia remains a major impediment to achieving optimal glycemic control in hospitalized patients. Healthcare institutions should have standardized treatment protocols that address mild, moderate and severe hypoglycemia.

INTRODUCTION

Diabetes increases the risk for disorders that predispose individuals to hospitalization, including cardiovascular disease (CVD), nephropathy, infection and lower-extremity amputations. The majority of hospitalizations for patients with diabetes are not directly related to the metabolic state, and diabetes management is rarely the primary focus of care. Therefore, glycemic control and other diabetes care issues are often not adequately addressed (1). A rapidly growing body of literature supports targeted glycemic control in the hospital setting, with potential for improved mortality, morbidity and healthcare economic outcomes (2).

The precise prevalence of diabetes in hospitalized adult patients is not known. One study reported a prevalence of 26% of known diabetes in hospitalized patients in a community teaching hospital (3). An additional 12% of patients had unrecognized diabetes or hospital-related hyperglycemia that reverted to normoglycemia after discharge. Diabetes has been reported to be the fourth most common comorbid condition listed on all hospital discharges (4).

ROLE OF ORAL ANTIHYPERGLYCEMIC AGENTS

No large studies have investigated the potential roles of various oral antihyperglycemic agents (OHAs) on outcomes in hospitalized patients with diabetes. However, OHAs may have a role in stable patients who had good glycemic control on OHAs prior to admission (unless newly developed condi-

tions, such as renal, hepatic or cardiac disturbances, represent contraindications to their use).

ROLE OF SUBCUTANEOUS INSULIN

Patients with type 1 diabetes must be maintained on insulin therapy during hospitalization to prevent diabetic ketoacidosis. Stable patients who are able to eat should typically receive the same dose of subcutaneous basal insulin (NPH, glargine, detemir) they were taking at home. Bolus (prandial) insulin (regular, lispro, aspart) may require adjustment depending on the patient's intercurrent illness and ability to consume meals. Correction-dose (supplemental) insulin is useful to treat unanticipated hyperglycemia in hospitalized patients (2,5). This involves the adjustment of the patient's usual scheduled or programmed insulin to compensate for unanticipated hyperglycemia. If correction doses are frequently required, the scheduled insulin doses should be increased. If patients are not able to eat their usual meals, prandial insulin doses might also need to be adjusted to avoid hypoglycemia.

Stable patients with type 2 diabetes using insulin at home should also continue their pre-admission insulin regimen, with adjustment as needed.

The use of “sliding scale” insulin therapy for inpatient management of diabetes is a common practice. Sliding scale insulin therapy treats hyperglycemia after it has occurred. Studies have shown that this reactive approach is associated with higher rates of hyper- and hypoglycemia (6).

ROLE OF INTRAVENOUS INSULIN INFUSION

Intravenous (IV) insulin infusion therapy should be considered during critical illness, or other illness requiring prompt glycemic control, or prolonged fasting (NPO status) (7). IV insulin infusion therapy should be administered only where frequent blood glucose (BG) monitoring and close nursing supervision are possible. Staff education is a critical component of the implementation of an IV insulin infusion protocol. IV insulin protocols should take into account the current and previous BG levels (and, therefore, the rate of change), and the patient's usual insulin dose. BG determinations should be performed every 1 to 2 hours until BG stability has been demonstrated.

For NPO patients not receiving enteral or parenteral

nutrition, dextrose infusions should be provided.

To maintain effective blood levels of insulin, short- or rapid-acting insulin should be administered 30 minutes to 2 hours before discontinuation of IV insulin infusion. The initial dose of subcutaneous insulin given after discontinuation of IV insulin infusion should be based on previously established dose requirements or the rate and pattern of in-hospital IV insulin infusion. Other parameters that affect subcutaneous insulin dose determination include body weight, stress of illness and other comorbid conditions such as renal insufficiency.

ORGANIZATION OF CARE

Healthcare institutions should implement a program to improve glycemic control in the inpatient setting. This should include the formation of a multidisciplinary steering committee to provide educational programs, implement policies to assess and monitor the quality of glycemic management, and produce standardized order sets, protocols and algorithms for diabetes care within the institution. The timely consultation of such teams has been demonstrated to improve quality, reduce length of stay and lower costs (8,9).

Self-management in the hospital may be appropriate for competent adult patients who successfully conduct self-management of diabetes at home, have a stable level of consciousness, and have the physical skills needed to self-administer insulin and perform self-monitoring of blood glucose (SMBG). A physician order for self-management should be written with respect to selection of food, SMBG, self-determination and administration of insulin dose and type.

Bedside BG monitoring

No study has compared the effect of frequency of bedside BG testing on the incidence of hyper- or hypoglycemia in the hospital. The frequency and timing of bedside BG monitoring should be individualized. Healthcare institutions must implement and maintain a quality-control program to ensure the accuracy of bedside BG testing (10,11).

Safety – hypoglycemia

Hypoglycemia remains a major impediment to achieving optimal glycemic control in hospitalized patients. Healthcare institutions should have standardized treatment protocols that address mild, moderate and severe hypoglycemia. Healthcare workers should be educated about factors that increase the risk of hypoglycemia, such as sudden reduction in oral intake or discontinuation of enteral or parenteral nutrition, unexpected transfer from nursing unit after rapid-acting insulin administration, and reduction in corticosteroid dose (12).

Safety – insulin administration errors

Insulin is identified as 1 of the top 5 “high-risk medications” in the hospital setting. A systems approach may work to

reduce errors. This includes preprinted, approved, unambiguous standard orders for insulin administration, or computerized order entry (13).

THE CRITICALLY ILL PATIENT

Acute hyperglycemia in the intensive care setting is not unusual and results from a number of factors, including stress-induced counterregulatory hormone secretion, and possibly the effect of medications administered in the intensive care unit (ICU) (14). Hyperglycemia in this setting has effects on multiple systems, including the CV, neurologic and immune systems (14). Van den Bergh and colleagues (15) demonstrated impressive benefits of intensive glycemic control with IV insulin infusion among predominantly surgical patients admitted to the ICU and requiring mechanical ventilation. A subsequent analysis of a heterogeneous ICU population with predominantly medical patients and utilizing historical controls demonstrated a reduction in mortality, length of stay, renal dysfunction and requirement of transfusion among those receiving intensive glycemic control with an IV insulin infusion protocol (16).

A meta-analysis of studies looking at the effects of insulin therapy for critically ill adult patients also demonstrated an overall reduction in mortality, particularly among those with diabetes and if glycemic control was a primary goal (17). However, this meta-analysis did not include any randomized controlled trials (RCTs) of intensive insulin therapy in a medical ICU. To date, there has been only 1 RCT of intensive insulin therapy and glycemic control among medical ICU patients (18). There was no difference in the primary outcome of in-hospital mortality between the groups. However, there was a significant reduction in the prespecified secondary outcomes of renal dysfunction, length of stay and prolonged mechanical ventilation. Mortality was increased among patients who stayed in the ICU for <3 days and decreased in patients who stayed in the ICU for >3 days.

Perioperative glycemic control

The management of individuals with diabetes at the time of surgery poses a number of challenges. Acute hyperglycemia is common secondary to the physiologic stress associated with surgery. Pre-existing diabetes-related complications and comorbidities may also influence clinical outcomes. Acute hyperglycemia has been shown to adversely affect immune function (19) and wound healing (20) in animal models. Observational studies in humans have shown that hyperglycemia increases the risk of postoperative infections (21-23) and renal allograft rejection (24), and is associated with increased resource utilization (25).

In patients undergoing coronary artery bypass surgery, a pre-existing diagnosis of diabetes has been identified as a risk factor for postoperative sternal wound infections, delirium, renal dysfunction, respiratory insufficiency and prolonged

hospital stay (26-28). Intraoperative hyperglycemia during cardiopulmonary bypass has been associated with increased morbidity and mortality rates in individuals with and without diabetes (29-31).

Studies investigating the role of diabetes as an independent risk factor for short- and long-term mortality rates post-coronary artery bypass surgery yield mixed results (26,32,33). Patients with known diabetes, undiagnosed diabetes and impaired fasting glucose identified by preoperative fasting plasma glucose (FPG) determination carry a higher risk of postoperative mortality than those with normal preoperative FPG levels (34). A diagnosis of diabetes may not influence early and midterm mortality in patients after off-pump coronary artery bypass (35).

In patients undergoing major noncardiac surgery, diabetes may increase the risk of postoperative complications, including mortality (36,37).

Major surgery

In patients undergoing coronary artery bypass surgery, improved intraoperative and postoperative glycemic control with a continuous IV insulin infusion or glucose insulin potassium (GIK) infusion to achieve plasma glucose (PG) levels between 5.5 and 10.0 mmol/L has been shown to decrease the rate of deep sternal wound infections and mortality (38-40). The use of GIK to maintain PG levels between 6.9 and 11.1 mmol/L was also associated with decreased rates of recurrent ischemia, atrial fibrillation and length of stay (40). However, among those without diabetes, tight intraoperative glycemic control initiated when PG levels rose above 5.6 mmol/L during coronary artery bypass surgery failed to decrease neurologic complications associated with the surgery (41). Among those with and without diabetes undergoing coronary artery bypass surgery, an RCT using a continuous IV insulin infusion to maintain intraoperative glycemic control between 4.4 and 5.6 mmol/L was compared with conventional intraoperative glycemic control (<11.1 mmol/L) (42). There was no additional benefit to more aggressive control.

Minor and moderate surgery

The appropriate perioperative glycemic targets for minor or moderate surgeries are less clear. There are few intervention studies assessing the impact of tight glycemic control on morbidity or mortality in these settings; however, a number of small studies that compared different methods of achieving glycemic control during minor and moderate surgeries did not demonstrate any adverse effects of maintaining perioperative glycemic levels between 5.0 and 11.0 mmol/L (43-45).

Rapid institution of perioperative control should be carefully considered in patients with poorly controlled type 2 diabetes undergoing monocular phacoemulsification cataract surgery with moderate to severe nonproliferative diabetic

retinopathy, because of the possible increased risk of postoperative progression of retinopathy and maculopathy (46). The outcome of vitrectomy does not appear to be influenced by perioperative control (47).

Given the data supporting tighter perioperative glycemic control during major surgeries and the compelling data showing the adverse effects of hyperglycemia, it is reasonable to target glycemic levels between 5.0 and 11.0 mmol/L for minor and moderate surgeries. However, the benefits of improved perioperative glycemic control must be weighed against the risk of perioperative hypoglycemia. Anesthetic agents and postoperative analgesia may alter the patient's level of consciousness and awareness of hypoglycemia. The risk of hypoglycemia can be reduced by frequent BG monitoring and carefully designed management protocols.

Acute stroke

Diabetes is well recognized as a major contributor to atherothrombotic cerebrovascular disease. About 21% of patients admitted with acute ischemic stroke have previously diagnosed diabetes; undiagnosed diabetes may increase the overall prevalence to >50% (48,49). Observational studies suggest that diabetes might increase the risk of mortality (50,51), infarct size or neurological impairment (49,50, 52,53) and reduce the benefit from acute thrombolytic revascularization (54). However, the results are inconsistent, and recent studies have failed to show an effect of diabetes on stroke morbidity or mortality (49,55).

Patients with diabetes who have higher BG values in the days following a cerebral infarction are more likely to exhibit infarct expansion, cerebral edema and worse short-term outcome (52,53). In 1 small study of 25 patients, mean PG levels >7.0 mmol/L were associated with increased infarct size (52). These observations indicate the need for studies to determine the effect of aggressive BG lowering in the early stages of stroke management.

A randomized trial performed on 933 patients with increased PG values (6.0 to 17.0 mmol/L) at the time of admission with acute stroke, compared the effect of GIK infusion with saline infusion. No reduction in mortality or significant disability at 90 days was observed, even though BG and blood pressure (BP) values were significantly better in the GIK group (56). This confirmed the findings of a smaller pilot study (57).

Patients with undefined neurological conditions admitted to an ICU and managed with IV insulin infusion to achieve intensive glycemic targets also showed no improvement in mortality compared to the control group (18).

At present, the apparent association between in-hospital hyperglycemia and adverse outcomes for ischemic stroke has not been accompanied by evidence that therapy to correct hyperglycemia is beneficial. In view of this, no specific recommendation regarding glycemic management during acute stroke can be made.

RECOMMENDATIONS

1. Provided that their medical conditions, dietary intake and glycemic control are acceptable, patients with diabetes should be maintained on their prehospitalization oral antihyperglycemic agents or insulin regimens [Grade D, Consensus].
2. For hospitalized patients with diabetes treated with insulin, a proactive approach that may include basal, prandial and correction-dose insulin, along with pattern management, is preferred over the "sliding scale" reactive approach using only short- or rapid-acting insulin [Grade D, Consensus].
3. To maintain intraoperative glycemic levels between 5.5 and 10.0 mmol/L for patients with diabetes undergoing coronary artery bypass surgery, a continuous IV insulin infusion alone [Grade C, Level 3 (38,39)] or with the addition of glucose and potassium [Grade B, Level 2 (40)], with an appropriate protocol and trained staff to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia, should be used.
4. A continuous IV insulin infusion should be used to achieve glycemic levels of 4.5 to 6.0 mmol/L in post-operative ICU patients with hyperglycemia (random PG >6.1 mmol/L) requiring mechanical ventilation to reduce morbidity and mortality [Grade A, Level 1A (15)], and in medical ICU patients with hyperglycemia (random PG >6.1 mmol/L) to reduce morbidity [Grade B, Level 2 (18)].
5. Perioperative glycemic levels should be maintained between 5.0 and 11.0 mmol/L for most other surgical situations, with an appropriate protocol and trained staff to ensure the safe and effective implementation of this therapy and minimize the likelihood of hypoglycemia [Grade D, Consensus].
6. In hospitalized patients, efforts must be made to ensure that patients using insulin or insulin secretagogues have ready access to an appropriate form of glucose at all times, particularly when NPO or during diagnostic procedures [Grade D, Consensus].
7. Measures to assess, monitor and improve glycemic control within the inpatient setting should be implemented, and include hypoglycemia management protocols and diabetes-specific discharge planning [Grade D, Consensus]. Glucagon should be available for any patient at risk for severe hypoglycemia when IV access is not readily available [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Pharmacologic Management of Type 2 Diabetes,

p. S53

Management of Acute Coronary Syndromes, p. S119

Treatment of Diabetes in Patients With Heart Failure,

p. S123

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Management of Obesity in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- An estimated 80 to 90% of persons with type 2 diabetes are overweight or obese.
- A modest weight loss of 5 to 10% of initial body weight can substantially improve insulin sensitivity and glycemic, blood pressure and lipid control.
- A comprehensive healthy lifestyle intervention program should be implemented in overweight and obese people with diabetes to achieve and maintain a healthy body weight. The addition of a pharmacologic agent should be considered for appropriate overweight or obese adults who are unable to attain clinically important weight loss with lifestyle modification.
- Adults with severe obesity may be considered for bariatric surgery when other interventions fail to result in achieving weight goals.

INTRODUCTION

An estimated 80 to 90% of persons with type 2 diabetes are overweight or obese. Furthermore, intensive insulin therapy is associated with weight gain (1). Weight loss has been shown to improve glycemic control by increasing insulin sensitivity and glucose uptake, and diminishing hepatic glucose output (2,3). The risk of death from all causes, cardiovascular disease (CVD) and some forms of cancer increases with excessive body fat (4). This relationship between increasing body fat accumulation and adverse health outcomes exists throughout the range of overweight and obese men and

women in all age groups, including those ≥ 75 years of age (5). While the relationship between increasing adiposity and adverse health effects has not been extensively examined in people with diabetes, it is likely that similar, if not greater, benefits are conferred on people with diabetes with lower body fat content or body mass index (BMI).

ASSESSMENT OF BODY WEIGHT

The initial assessment of people with diabetes should include height and weight measurements, calculation of BMI (kg/m^2) (see Table 1) (6), and waist circumference (WC) to assess the degree of abdominal fat (Table 2) (6). Metabolic comorbidities, such as hypertension, dyslipidemia and CVD, should also be assessed since they are highly correlated with increasing BMI (7,8). Excessive upper body fat, or abdominal obesity, is a strong independent predictor of metabolic comorbidities (9,10). Cutoff values for WC vary among expert guidelines. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines (11,12) and Health Canada (6) identify WC values ≥ 102 cm (40 inches) in men and ≥ 88 cm (35 inches) in women as being associated with substantially increased abdominal fat accumulation and health risks (Table 2). The International Diabetes Federation (13) has proposed population-specific WC cutoff values that are associated with increased risk of complications and are lower than the NCEP-ATP III guidelines (Table 3) (13). Neither set of WC values has been fully validated against the development of clinical events, and considerable population-based research is needed in this area.

Table 1. Canadian Guidelines for Body Weight Classification in Adults using BMI (6)

Classification	BMI* category (kg/m^2)	Risk of developing health problems
Underweight	<18.5	Increased
Normal weight	18.5–24.9	Least
Overweight	25.0–29.9	Increased
Obese	≥ 30.0	
Class I	30.0–34.9	High
Class II	35.0–39.9	Very high
Class III	≥ 40.0	Extremely high

*BMI values are age and gender independent, and may not be correct for all ethnic populations

BMI = body mass index

Table 2. WC and risk of developing health problems (6)

WC cutoff points*†	Risk of developing health problems
Men ≥ 102 cm (40 inches)	Increased
Women ≥ 88 cm (35 inches)	Increased

*WC cutoffs may be lower in some populations (e.g. older individuals, Asian population [See Table 3]), especially in the presence of the metabolic syndrome (such as hypertriglyceridemia)

†Increased WC can also be a marker for increased risk, even in persons with normal weight

WC = waist circumference

TREATMENT OF OBESITY

The goals of therapy for overweight and obese people with diabetes are to reduce body fat, attain and maintain a healthy or lower body weight for the long term, and prevent weight regain. In general, obese people with diabetes have greater difficulty with weight loss compared to similarly obese people without diabetes (14). A modest weight loss of 5 to 10% of initial body weight can substantially improve insulin sensitivity, glycemic control, high blood pressure (BP) and dyslipidemia (15-19). The optimal rate of weight loss is 1 to 2 kg/month. A negative energy balance of 500 kcal/day is typically required to achieve a weight loss of 0.45 kg/week (20).

Lifestyle interventions

Lifestyle intervention is recommended for weight loss in order to improve health status and quality of life (20,21). In people with diabetes who are overweight or obese, achieving a healthy weight through an active lifestyle promotes a general sense of well-being and cardiovascular (CV) fitness, along with other benefits, such as reducing CVD, morbidity,

mortality and other complications attributable to obesity (22). Lifestyle interventions that combine dietary modification, increased and regular physical activity and behaviour therapy are the most effective (23-25). Structured interdisciplinary programs have demonstrated the best short- and long-term results (24). Ongoing follow-up with the healthcare team is important to plan individualized dietary and activity changes to facilitate weight loss. Adjustments to anti-hyperglycemic agents may be required as the individual with diabetes loses weight (26).

All weight-loss diets must be well balanced and nutritionally adequate to ensure optimal health. In general, a carbohydrate intake of at least 100 g/day is required to spare protein breakdown and muscle wasting, and to avoid large shifts in fluid balance and ketosis. High-fibre foods that take longer to eat and digest are associated with greater satiety. Adequate protein intake is required to maintain lean body mass and other essential physiological processes. Reduced intake of saturated fat and energy-dense foods should be emphasized to achieve the required daily energy deficit to promote weight loss. Very low-calorie diets with <900 kcal/day are not recommended, except under medical supervision.

Because confusion over portion size of foods and beverages (27) may lead to overeating, people with diabetes should be counselled by a dietitian on appropriate serving sizes and on how to select meals, preferably nutrient-rich meals (i.e. containing whole grains and legumes), which are associated with greater satiety and lower caloric intake (28).

Behavioural therapy

Two large-scale reviews of >100 individual studies evaluating behaviour modification techniques support their effectiveness in promoting weight loss as adjuncts to lifestyle intervention (29,30).

Members of the healthcare team should consider using a structured approach to providing advice and feedback on physical activity, healthy eating habits and weight loss (31-34).

Table 3. Ethnic-specific values for WC (13)

Country or ethnic group	Central obesity as defined by WC	
	Men	Women
Europid*	≥ 94 cm	≥ 80 cm
South Asian, Chinese, Japanese	≥ 90 cm	≥ 80 cm
South and Central American	Use South Asian cutoff points until more specific data are available	
Sub-Saharan African	Use Europid cutoff points until more specific data are available	
Eastern Mediterranean and Middle East (Arab)	Use Europid cutoff points until more specific data are available	

*NCEP-ATP III guidelines (11,12) and Health Canada (6) define central obesity as WC values ≥ 102 cm (40 inches) in men and ≥ 88 cm (35 inches)

WC = waist circumference

Pharmacotherapy

Pharmacotherapy for overweight people with diabetes not only improves glycemic control, but also results in a significant reduction in the doses of antihyperglycemic agents (26). Pharmacotherapy is an acceptable adjunct in the short- and long-term management of obesity when lifestyle measures fail to achieve the desired weight loss after an adequate trial of 3 to 6 months (20,35). Pharmacotherapy can be considered for people with BMI ≥ 30.0 kg/m² with no obesity-related comorbidities or risk factors, or BMI ≥ 27.0 kg/m² with obesity-related comorbidities or risk factors (20). Antiobesity drug therapy may be considered as an adjunct to nutrition therapy, physical activity and behaviour modification to achieve a target weight loss of 5 to 10% of initial body weight and for weight maintenance (20,35).

Two medications, orlistat and sibutramine, have been approved in Canada for long-term management of obesity (Table 4). Drug therapy leads to even greater weight loss when coupled with lifestyle intervention and behaviour modification therapy. Both drugs have been shown to be effective in obese people with type 2 diabetes, improving glycemic and metabolic control, and resulting in favourable changes in lipid levels, BP profile and fat distribution (26,36,37). In obese people with impaired glucose tolerance (IGT), orlistat also improves glucose tolerance and reduces the progression to type 2 diabetes (38). Clinical trials with antiobesity agents have confirmed a smaller degree of weight loss in people with diabetes compared with obese people who do not have diabetes (14,26).

When pharmacotherapy is being considered in the treatment of the obese or overweight person with type 2 diabetes, the choice of drug should be based on the individual's CV risk profile, dietary habits and concomitant disease(s).

People with irregular eating habits, such as those who "snack" frequently, may be better suited to sibutramine therapy because of its long-acting satiety-enhancing properties. Combining orlistat and sibutramine therapy is not advocated for clinical use. Sibutramine should be avoided in patients with ischemic heart disease, congestive heart failure or other major cardiac disease. Orlistat should be avoided in patients with inflammatory or other chronic bowel disease.

Other available antiobesity drugs, such as diethylpropion and phentermine, are sympathomimetic noradrenergic appetite suppressants that are approved only for short-term use of a few weeks. They are not recommended because of modest efficacy and frequent adverse side effects.

Currently, a number of new molecular entities that target receptors and metabolic processes relevant to energy metabolism are being developed for the treatment of obesity. Among these emerging strategies, cannabinoid type 1 receptor antagonists currently appear to be the most promising (39).

Surgery

Individuals who are candidates for surgical procedures should be carefully selected after evaluation by an interdisciplinary team with medical, surgical, psychiatric and nutritional expertise. Surgery is usually reserved for people with class III obesity (BMI ≥ 40.0 kg/m²), or class II obesity (BMI=35.0–39.9 kg/m²) in the presence of comorbidities (40) and the inability to achieve weight-loss goals following an adequate trial of lifestyle intervention. Long-term, if not lifelong, medical surveillance after surgical therapy is necessary for most people. Preferred surgical options for weight loss include laparoscopic vertical banded gastroplasty and laparoscopic Roux-en-Y gastric bypass (41-43).

Table 4. Medications approved for the treatment of obesity in type 2 diabetes

Class	Generic (trade) name	Recommended regimen	Action	Adverse effects
Gastrointestinal lipase inhibitor	orlistat (Xenical)	120 mg TID (during or up to 1 hour after each meal)	<ul style="list-style-type: none"> • Nonsystemic pancreatic lipase inhibitor that exerts its therapeutic activity in the stomach and gastrointestinal tract by reducing dietary fat digestion and absorption by about 30% 	<ul style="list-style-type: none"> • Abdominal bloating, pain and cramping • Steatorrhea • Fecal incontinence
Norepinephrine and serotonin reuptake inhibitor	sibutramine (Meridia)	10–15 mg OD (in the morning)	<ul style="list-style-type: none"> • Reduces food intake by enhancing satiety • May increase thermogenesis • May prevent decline in energy expenditure with weight loss 	<ul style="list-style-type: none"> • Xerostomia • Increase heart rate and blood pressure • Constipation • Dizziness

RECOMMENDATIONS

1. A comprehensive healthy lifestyle intervention program (including a hypocaloric, nutritionally balanced diet, regular physical activity or exercise, and behavioural modification techniques) for overweight and obese people with, or at risk for diabetes, should be implemented to achieve and maintain a healthy body weight [Grade D, Consensus]. Members of the healthcare team should consider using a structured approach to providing advice and feedback on physical activity, healthy eating habits and weight loss [Grade C, Level 3 (31-34)].
2. In overweight or obese adults with type 2 diabetes, a pharmacologic agent such as orlistat [Grade A, Level 1A (26)] or sibutramine [Grade B, Level 2 (37)] should be considered as an adjunct to lifestyle modifications to facilitate weight loss and improve glycemic control.
3. Adults with class III obesity (BMI ≥ 40.0 kg/m²) or class II obesity (BMI 35.0 to 39.9 kg/m²) with other comorbidities may be considered for bariatric surgery when other lifestyle interventions are inadequate in achieving weight goals [Grade C, Level 3 (43)].

OTHER RELEVANT GUIDELINES

Physical Activity and Diabetes, p. S37

Nutrition Therapy, p. S40

RELATED WEBSITES

Health Canada. Canadian Guidelines for Body Weight Classification in Adults. Quick Reference for Professionals. Available at: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/cg_quick_ref-ldc_rapide_ref_e.pdf. Accessed September 1, 2008.

OBESITY CANADA GUIDELINES

2006 Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children. Available at: <http://www.cmaj.ca/cgi/content/full/176/8/S1/DC1>. Accessed September 1, 2008.

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Psychological Aspects of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Significant behavioural demands and challenging psychosocial factors affect nearly all aspects of diabetes management and subsequent glycaemic control.
- All individuals with diabetes and their families should be regularly screened for symptoms of psychological distress.
- Preventive interventions such as participative decision-making, feedback and psychological support should be incorporated into all primary care and self-management education interventions to enhance adaptation to diabetes and reduce stress.

INTRODUCTION

Significant behavioural demands and challenging psychosocial factors affect nearly all aspects of diabetes management and subsequent diabetes control (1,2). Psychological issues related to the diagnosis and/or self-care demands may present anywhere on a continuum from impairment in quality of life to clinically significant depressive and/or anxiety disorders.

ADJUSTMENT PROBLEMS

Both adults and children face challenges associated with adjustment to diabetes. Some children and/or their parents have adjustment problems soon after the diagnosis of diabetes (3,4). Those who do not solve these problems within the first year of diagnosis are at risk for poor adaptation to diabetes, including regimen adherence problems, poor glycaemic control and continued psychosocial difficulties (5,6). Stress (general and diabetes-specific) (7,8), inadequate social and family interactions (9,10), inappropriate beliefs about the nature of diabetes (10), and poor coping skills (11,12) may have a negative impact on self-care behaviours and glycaemic control.

Adults with type 1 and 2 diabetes across many cultures report significant psychological distress related to the diagnosis of diabetes, with a negative impact on diabetes self-management (13).

The diagnosis of diabetes may precipitate or exacerbate existing psychological disorders (14,15). As quality of life is adversely affected by the presence of comorbid psychological disorders and health complications (14,15), the identi-

cation of potential psychiatric conditions, such as depression, anxiety and eating disorders, is critical.

Depression

Depressive symptoms are common in people with diabetes compared with the general population (14,16,17), and major depressive disorder is present in approximately 15% of patients with diabetes (18). Depressive disorders in adults and children are associated with poorer self-care behaviour (19,20), poorer glycaemic control, health complications, decreased quality of life and psychological well-being (14,21), increased family problems, and higher healthcare costs (22-25).

Anxiety

Emerging evidence suggests that the prevalence of phobic disorders (24,26) and generalized anxiety disorders (3) is elevated in people with type 1 diabetes. Generalized anxiety disorder appears to be increased in individuals with diabetes compared with the general population (14 vs. 3 to 4%, respectively) (27). As many as 40% of patients have at least some anxiety symptoms (27), and fear of hypoglycemia (28,29) is not uncommon in those with diabetes. A recent meta-analysis suggested that the presence of clinically significant anxiety disorders among those with type 1 and 2 diabetes is associated with poor glycaemic control (28).

Eating disorders

Eating disorders are frequently observed in young women and adolescent females with type 1 diabetes (30,31) and are associated with poorer glycaemic control (31,32) and an increased risk of long-term complications (33). A meta-analysis of controlled studies of eating disorders and diabetes showed a higher prevalence of bulimia in girls with diabetes compared with healthy controls (34). Other studies have demonstrated prevalence rates of full syndrome and subthreshold eating disorders that are twice as high as those in peers without diabetes (30,35). Young women and adolescent females with type 1 diabetes should, therefore, be regularly screened for eating disorders with the Eating Disorders Inventory (36). Those with an identified or suspected eating disorder should be referred to a medical team or mental health professional knowledgeable in treating such disorders.

SCREENING

All individuals with diabetes and their families should be regularly screened for symptoms of psychological and social distress (2,20). Healthcare professionals should actively explore psychological factors by asking empathetic but frank open-ended questions about stress, social support, unhealthy self-care behaviours, health beliefs about risk of complications, treatment efficacy and the degree of interference with normal functioning (37). People with diabetes should be screened for depression and anxiety regularly, either through direct queries (e.g. "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "During the past month, have you often been bothered by little interest or pleasure in doing things?") (38), or with a standardized questionnaire (e.g. Beck Depression Inventory [39], the Problem Areas in Diabetes scale [37], the Child Health Questionnaire [CHQ] [40], Behaviour Assessment System for Children [BASC] [40]).

INTERVENTIONS

Preventive psychological interventions should be incorporated into all primary care and self-management education interventions to enhance adaptation to diabetes and reduce stress. Educational and psychological interventions often share a theoretical basis around increasing readiness to change and self-efficacy (41,42).

Effective interventions for children and adults include psychosocial support, feedback and reinforcement (20,43-45); coping skills training (46); cognitive-behavioural therapy (CBT) (47); and family behaviour therapy (48). Approaches that increase patient participation in decision-making regarding care and education have been shown to be more effective than a "do as I say" approach in enhancing psychological adjustment to diabetes, and potentially preventing psychological distress (49-51).

For those with suboptimal self-care or significant psychological symptoms, focused interventions using CBT or family behaviour therapy need to be considered (43,52). These issues should be addressed using psychosocial services within diabetes teams or resources in the community. In pediatric populations, intensive case management with psychoeducation may be required (43,52). In-home, multisystemic therapy can be used to reduce diabetes-related stress (53), improve glycemic control and reduce inpatient admissions for adolescents with poor glycemic control (2,54). Antidepressant medication (55) and CBT have each been shown to be specifically effective in treating depression in adults with diabetes (56). Risk of significant weight gain during extended use of selective serotonin reuptake inhibitor antidepressants may be greater for paroxetine (57); sertraline or fluoxetine may be preferred in this weight-sensitive population.

RECOMMENDATIONS

1. Individuals with diabetes should be regularly screened for subclinical psychological distress and psychiatric disorders (e.g. depressive and anxiety disorders) by interview [Grade D, Consensus] or with a standardized questionnaire [Grade B, Level 2 (39)].
2. Patients diagnosed with depression, anxiety or eating disorders should be referred to mental health professionals who are either part of the diabetes team or are in the community [Grade D, Consensus]. Those diagnosed with depression should be offered treatment with CBT [Grade B, Level 2 (56)] and/or antidepressant medication [Grade A, Level 1A (55)].
3. Multidisciplinary team members with required expertise should offer CBT-based techniques, such as stress management strategies and coping skills training [Grade A, Level 1A for type 2 diabetes (42); Grade B, Level 2, for type 1 diabetes (46)], family behaviour therapy [Grade B, Level 2 (48,53)] and case management [Grade B, Level 2 (43,53)] to improve glycemic control and/or psychological outcomes in individuals with suboptimal self-care behaviours, suboptimal glycemic control and/or psychological distress.

OTHER RELEVANT GUIDELINES

Organization of Diabetes Care, p. S20

Self-management Education, p. S25

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

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Influenza and Pneumococcal Immunization

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Vincent Woo MD FRCPC

KEY MESSAGES

- Studies in high-risk individuals, which included people with diabetes, have shown that influenza vaccination can reduce hospitalizations by approximately 40%.
- As people with diabetes are at least as susceptible to pneumococcal infection as other people with chronic diseases, the use of the pneumococcal vaccine is encouraged.
- A one-time pneumococcal revaccination is recommended for individuals >65 years of age if the original vaccine was administered when they were <65 years of age and >5 years earlier.

INTRODUCTION

People with diabetes, especially those with renal and cardiac complications, are at high risk for morbidity and mortality from influenza and pneumococcal disease (1). Studies in high-risk individuals, which included people with diabetes, have shown that influenza vaccination can reduce hospitalizations by about 40% (2). However, there are few randomized controlled trials that have specifically evaluated the use and benefit of influenza or pneumococcal immunization in people with diabetes (1). Clinical practice recommendations for people with diabetes must therefore be extrapolated from recommendations for individuals at high risk of complications associated with these infectious diseases (3-5).

INFLUENZA IMMUNIZATION IN ADULTS

The majority of studies on influenza immunization rely on observational reports of increased death rates in people with diabetes during influenza epidemics (6-9). One case-control study of people with diabetes showed a 6-fold increased risk of hospitalization during influenza outbreaks compared to non-epidemic years (9).

A retrospective case-control study demonstrated the effectiveness of influenza vaccination in reducing rates of hospitalization of people with diabetes for influenza, pneumonia or diabetes-related events during 2 influenza epidemics in Leicestershire, England, United Kingdom (10). The study detected a 79% reduction in hospitalization rates during the 2 epidemics in people with diabetes who had been immunized against influenza during the period immediately preceding the epidemic. Another nested case-control study in the Netherlands demonstrated that vaccination was associ-

ated with a 56% reduction in any complication, a 54% reduction in hospitalizations and a 58% reduction in deaths in people with type 2 diabetes (11).

PNEUMOCOCCAL IMMUNIZATION IN ADULTS

Numerous studies have demonstrated the efficacy of immunization in reducing pneumococcal bacteremia in the general population (12-15). There is widespread acceptance that people with diabetes are at least as susceptible to pneumococcal infection as other people with chronic diseases (1), and therefore the use of the pneumococcal vaccine is encouraged in this population. A one-time revaccination is recommended for individuals >65 years of age if the original vaccine was administered when they were <65 years of age and >5 years earlier.

RECOMMENDATIONS

1. People with diabetes should receive an annual influenza vaccine to reduce the risk of complications associated with influenza epidemics [*Grade D, Consensus*].
2. People with diabetes should be considered for vaccination against pneumococcus [*Grade D, Consensus*].

RELATED WEBSITES

National Advisory Committee on Immunization. *Canadian Immunization Guide*. 7th ed. Ottawa, ON: Canadian Medical Association; 2006. Available at: <http://www.phac-aspc.gc.ca/publicat/cig-gci/index.html>. Accessed September 1, 2008.

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Pancreas and Islet Transplantation

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Breay W. Paty MD FRCPC, Erin Keely MD FRCPC and Charlotte McDonald MD FRCPC

KEY MESSAGES

- Pancreas transplant can result in prolonged insulin independence and a possible reduction in the progression of secondary complications of diabetes.
- Islet transplant can result in transient insulin independence and can reliably stabilize blood glucose concentrations in people with glycemic lability.
- The risks of chronic immunosuppression must be carefully weighed against the potential benefits of pancreas or islet transplant for each individual.

INTRODUCTION

Beta cell replacement as a means of restoring endogenous insulin secretion, either by whole organ pancreas transplant or islet transplant, has a number of potential advantages over standard exogenous insulin therapy for the treatment of type 1 diabetes, including improved glycemic control and the potential for insulin independence. However, any advantages must be weighed against the risks and adverse effects of surgery and chronic immunosuppressive therapy that accompany these treatments. Unfortunately, the absence of data from randomized controlled trials (RCTs) makes it difficult to draw firm conclusions regarding the efficacy of these therapies compared with intensive medical management of diabetes. Nevertheless, some general recommendations can be made regarding the role of pancreas and islet transplant in the context of current clinical experience.

WHOLE PANCREAS TRANSPLANTATION

Pancreas transplantation has progressed significantly in terms of surgical technique and immunosuppression since it was first introduced in the 1960s (1). It is most commonly categorized on the basis of the presence or absence of a kidney transplant and the relative timing of the procedures: simultaneous pancreas kidney (SPK) transplant; pancreas after kidney (PAK) transplant; or pancreas transplant alone (PTA), in the absence of a kidney transplant. Worldwide, non-controlled pancreas graft and patient survival rates differ slightly among these 3 categories (2). However, in the absence of large RCTs, it is unclear whether these differences are clinically significant.

Metabolic studies demonstrate a marked improvement in glycemic control and glycated hemoglobin (A1C) after suc-

cessful whole pancreas transplant, with most recipients achieving insulin independence that can last for many years (3,4). A reduction in albuminuria has been shown at 1 year posttransplant (5). Similarly, improvements in the histologic changes of diabetic nephropathy have been reported after 5 to 10 years posttransplant (6). Studies also show an improvement and/or stabilization of diabetic retinopathy (7) after an initial risk of worsening due to a rapid reduction in glycemia (8). The benefits of pancreas transplant are less clear in patients with advanced retinal disease (9). Peripheral sensory and motor neuropathies have been shown to improve after pancreas transplant (10,11). Improvements in autonomic neuropathy are less consistent and may take longer to achieve (12,13). There is growing evidence that pancreas transplant improves cardiovascular (CV) function (14) and may reduce cardiac events (15). However, studies have generally been small and nonrandomized. It remains uncertain whether pancreas transplant improves overall mortality rates (16). Finally, diabetes-related quality of life appears to improve after pancreas transplant, although overall quality of life may not change (17).

ISLET TRANSPLANTATION

Islet transplantation is a less invasive procedure than pancreas transplantation. It involves the infusion of islets isolated from cadaveric pancreata via the portal vein into the liver (18). Unlike whole pancreas transplant recipients, most islet transplant recipients require at least 2 islet infusions to achieve insulin independence, although there has been recent short-term success using single islet donors in some centres (19). The rate of posttransplant insulin independence at the most experienced centres is approximately 80% at 1 year, but declines to about 10% at 5 years (20-22). Rates of insulin independence may be lower at less experienced centres (23,24). Most transplant recipients continue to have some endogenous insulin secretion even after insulin independence is lost. However, there are very few long-term data regarding function of the transplanted islets after 5 years. Most published studies involve islet transplant in the absence of a kidney transplant (islet transplant alone [ITA]). There is some evidence suggesting that islet transplant performed at the same time as a kidney transplant (simultaneous islet kidney [SIK]) or after a kidney transplant (islet after kidney [IAK]) may have comparable results (25,26).

The principal benefit of islet transplant is stabilization of blood glucose control in individuals with severe glycemic lability or hypoglycemia unawareness. This benefit is evident and persists in most recipients, even in the absence of insulin independence (27,28). The impact of islet transplantation on diabetes complications remains uncertain. Renal function appears to decline after ITA in patients with significant pre-existing renal dysfunction, although the degree of decline can vary (29,30). For this reason, particular caution may be warranted for patients with pre-existing renal dysfunction. There is some evidence that IAK transplant recipients show improved endothelial and CV function compared to kidney transplant recipients (31,32). Kidney graft survival rates also appear to improve with concomitant islet transplant (33). The impact of islet transplantation on diabetic retinopathy and neuropathy is still uncertain. Quality of life appears to improve initially after islet transplantation, due primarily to a reduced fear of hypoglycemia, but declines with the loss of insulin independence (34,35).

RISKS OF PANCREAS AND ISLET TRANSPLANTATION

Pancreas transplantation is associated with significant perioperative risks, including graft pancreatitis, peripancreatic abscess, duodenal stump leak, venous or arterial thrombosis, and conversion from bladder to enteric drainage (36). Islet transplantation is associated with fewer procedural risks, which may include intraperitoneal hemorrhage, partial portal vein thrombosis, gallbladder puncture and a transient elevation of liver enzymes (37). Both pancreas and islet transplantation require chronic immunosuppression, which is associated with a number of risks and side effects, including increased risk of infection and malignancy, nephrotoxicity, diarrhea, oral ulcers (in the case of islet transplant) and many others. These risks must be carefully weighed against the potential benefits of transplant for each individual.

RECOMMENDATIONS

1. For individuals with type 1 diabetes and end-stage renal disease who are undergoing or have undergone successful kidney transplant, pancreas transplant should be considered [Grade D, Consensus].
2. For individuals with type 1 diabetes and preserved renal function, but with persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia unawareness despite best efforts to optimize glycemic control, pancreas transplant [Grade D, Level 4 (4)] or islet transplant [Grade D, Level 4 (21)] may be considered.

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Complementary and Alternative Medicine in the Management of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Jeannette Goguen MD MEd FRCPC

KEY MESSAGES

- Up to 30% of patients with diabetes use complementary and alternative medicine (CAM) for various indications.
- Most CAM studies have small sample sizes and are of short duration, and therefore may have missed harmful side effects.
- Certain CAM in common use for disorders other than diabetes can result in side effects and drug interactions.

INTRODUCTION

Complementary and alternative medicine (CAM) has been defined as “medicine that does not conform to the standards of the medical community, is not widely taught in North American medical schools and is not available in North American hospitals” (1). It involves the use of herbal medications as well as dietary supplements, including minerals, vitamins and other micronutrients. When used in a traditional system (e.g. Chinese, Tibetan, Ayurvedic), an herb is often only one of a number of interventions, which could also include acupuncture, yoga and multiple other herbs.

MANAGEMENT

CAM in the management of diabetes has been included in these guidelines, as it includes potential new therapeutic agents, and because studies have suggested that up to 30% of patients with diabetes use CAM for multiple indications (2), leading to potential side effects, drug interactions and increased cost to the patient. In 1 Canadian study in predominantly Caucasian subjects, the most commonly used alternative trace element for glycemic control was chromium (6%), followed by magnesium (2.2%) and vanadium (1%) (2). Herbs were rarely used.

There are several issues unique to CAM that have implications in the assessment of the evidence for its use: trials are typically of short duration, with small sample sizes and unique patient populations that may not be generalizable (3); publications are often difficult to access, with only 10% referenced in MEDLINE (4); and there is a lack of standardization and purity of available compounds, including their contamination with regular medications and toxic compounds (5).

The following herbs have been shown to improve glycemic control in adults with type 2 diabetes: *Aloe vera* (6,7); *Ipomoea*

batatas (caiaipo) (8); *Coccinia indica* (9); *Ganoderma lucidum* (10); *Gymnema sylvestre* (11); *Ocimum tenuiflorum* (holy basil or tulsi) (12); *Salacia reticulata* (13); pinitol (14); touchi (15); and *Pterocarpus marsupium* (vijayasar) (16). However, as all of the studies were small and of short duration, it is premature to recommend the use of these agents.

The following herbs have been shown to be ineffective for glycemic control in adults with type 2 diabetes: *Syzygium cumini* (17); *Tinospora crispa* (18); French maritime pine bark (19); garlic (20); and soy phytoestrogens (21). The following dietary supplements have been shown to be ineffective: coenzyme Q10 (22) and vitamin E (23-26). Glucosamine sulfate, used to treat osteoarthritis, does not affect glycemic control (27).

The following herbs have conflicting evidence with regards to glycemic control in adults with type 2 diabetes: *Cinnamomum cassia* (Chinese cinnamon) (28-31); *Momordica charantia* (bitter melon or bitter gourd) (32,33); *Trigonella foenum-graecum* (fenugreek) (34,35); and ginseng (36,37). The following dietary supplements have conflicting evidence: chromium (38-46); vanadium (47); magnesium (48-52); lipoic acid (53); vitamin C (52,54); and carnitine (55,56).

Studies have examined the combinations of herbs as used by traditional practitioners. These studies included Tibetan traditional medicine (57), Chinese plants (58,59) and Ayurvedic pancreas extract (60). Methodological concerns make the results of these studies difficult to interpret.

COMPLICATIONS

It is important to consider potential harm from the use of CAM. Most studies were of small sample size and short duration, and thus may have missed harmful side effects. The use of *Tinospora crispa* was associated with markedly elevated liver enzymes in 2 patients and should be avoided (18). Alternative medications should not be used in pregnancy – some are abortifacients (e.g. *Momordica charantia*) (61). As well, there are case reports of severe hypoglycemia with the use of bitter melon in children (61).

Impurities of substances are another concern. Contamination with regular medications and with heavy metals has been documented in several publications (5). Finally, certain CAM in common use for disorders other than diabetes can result in side effects and drug interactions. Agents that have been associated with elevations in blood pressure include the following: ginseng, licorice, yohimbine

and yerba mate. It is important to be aware of the following drug interactions: *Hypericum perforata* (St John's wort) (used in depression) induces CYP3A4 and can reduce levels of statins cleared by this mechanism; *Ginkgo biloba* (used for Alzheimer's disease and intermittent claudication) reduces platelet aggregation and can potentiate other medications that affect bleeding; psyllium can retard the absorption of some drugs and minerals.

For a more detailed discussion of CAM and diabetes, see the review by Yeh and colleagues (62).

RECOMMENDATIONS

1. At this time, CAM is not recommended for glycemic control for individuals with diabetes, as there is not sufficient evidence regarding safety and efficacy [Grade D, Consensus].
2. Individuals with diabetes should be routinely asked if they are using CAM [Grade D, Consensus].

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Identification of Individuals at High Risk of Coronary Events

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes increases the prevalence of coronary artery disease (CAD) approximately 2- to 3-fold compared to individuals without diabetes. People with diabetes develop CAD 10 to 12 years earlier than individuals without diabetes. When a person with diabetes has an acute coronary event, the short- and long-term outcomes are considerably worse than for the person without diabetes.
- People with diabetes should be considered to have a high 10-year risk of CAD events if ≥ 45 years and male, or ≥ 50 years and female. For the younger person (male < 45 years or female < 50 years) with diabetes, the risk of developing CAD may be assessed from the evaluation of risk factors for CAD (both classical and diabetes-related).
- When assessing the need for pharmacologic measures to reduce risk in the younger person with diabetes, it is important to consider his or her high lifetime risk of developing CAD.

INTRODUCTION

Diabetes increases the prevalence of coronary artery disease (CAD) approximately 2- to 3-fold compared to individuals without diabetes (1-3). Coronary and cerebrovascular events are responsible for $>75\%$ of the deaths in people with diabetes, and are 40 times more likely to occur than the serious consequences of microvascular disease such as end-stage renal failure (4). When a person with diabetes has an acute coronary event, the short- and long-term outcomes are considerably worse than for the person without diabetes (5,6).

Individuals at high risk of cardiovascular (CV) morbidity and mortality should receive pharmacologic vascular protective measures such as statin and angiotensin-converting enzyme (ACE) inhibitor or angiotensin II antagonist (ARB) therapy and acetylsalicylic acid (ASA) therapy. The “high-risk” threshold for dyslipidemia treatment in the general population is defined as the level of risk for hard CAD events observed in people with established CAD – a mean 20% 10-year risk of cardiac death or nonfatal myocardial infarction (MI) (7,8). Although a high proportion of people with diabetes are at high risk for CAD (9) over a 10-year period, it is recognized that some do not have a risk equivalent to a person with established CAD (10,11). The definitions of

“high risk” established in this section are those used in the present guidelines for dyslipidemia treatment and ACE inhibitor or ARB therapy and ASA therapy.

RISK FACTORS

Age is the most powerful overall predictor of CAD risk. In the general population, the average male will reach a 20% 10-year risk of a CAD event by age 60, the average female by age 65. Diabetes confers a risk that is equivalent to aging approximately 15 years, with a transition from intermediate risk to high risk in men at age 47.9 years, and in women almost 7 years later at age 54.3 years (2). It is therefore recommended that people with diabetes be considered at high risk if ≥ 45 years and male, or ≥ 50 years and female. For the younger person (male < 45 years or female < 50 years) with diabetes, the risk of developing CAD may be assessed from the evaluation of risk factors for CAD (both classical and diabetes-related).

Classical risk factors for CAD, such as smoking, hypertension and hyperlipidemia (elevated low-density lipoprotein cholesterol [LDL-C] and low high-density lipoprotein cholesterol), add to the risk conferred by diabetes alone (12). Diabetes-related risk factors such as duration of diabetes >15 years (13) and hyperglycemia (as determined by glycated hemoglobin [A1C] levels [14]), as well as the presence of microvascular disease (micro- or macroalbuminuria [15], impaired renal function [16] or retinopathy [17]) and features of metabolic syndrome (18), add to the risk of premature CAD events.

Type 1 diabetes is an independent risk factor for premature CVD and mortality in young adults (20 to 39 years) (19). The presence of CAD in people with type 1 diabetes is related to age, duration of diabetes, presence of retinopathy, higher A1C levels and higher albumin excretion rates, as well as to traditional CAD risk factors such as elevated total cholesterol and LDL-C cholesterol, smoking and excess body weight (20). A recent study (21) showed that for all age groups, the majority of people with type 1 diabetes had at least 1 CV risk factor. Even if an individual with type 1 diabetes has a low short-term risk of a CV event (i.e. younger and shorter duration of diabetes), his/her long-term risk is very high. In the absence of firm data on risk, individuals are classified as high-risk if >30 years old with a duration of diabetes of >15 years.

Subclinical vascular disease is common in people with diabetes (22), and the detection of unrecognized disease will immediately place a person at a high risk for CAD events. A history of chest discomfort, unexplained dyspnea, exertional leg pain (23) or erectile dysfunction (24-26) may indicate CAD or peripheral arterial disease. The presence of a carotid or femoral bruit or a low ankle brachial index (27) suggests vascular disease, and a duplex ultrasound study should be considered to establish the presence of atherosclerotic disease. Measurement of the carotid intima thickness (28) and detection of coronary calcification (29-31) and silent myocardial ischemia (32) are additional tests that can be considered in the person at risk. However, their role in the routine screening of the younger person with diabetes for risk stratification is not yet established.

RISK TABLES

Risk tables and equations such as the UKPDS allow the calculation of the absolute global risk of a coronary or CV event for an individual with type 2 diabetes with no prior history of MI or stroke (33). In the future, the SCORE risk engine (34) may be valuable in helping clinicians establish absolute vascular risk for a Canadian population. Other available risk tables, such as PROCAM (35), the CV Life Expectancy Model (36) and the Strong Heart Study (37), have limitations that may reduce their accuracy to predict outcomes, especially in a younger population with diabetes.

RISK MANAGEMENT OF PATIENTS WITH DIABETES WITHOUT CVD

Strategies to reduce CV events by initiating pharmacologic vascular protective measures could include the following: 1) a population health strategy of treating all patients with diabetes; 2) a baseline risk strategy of treating only patients at moderate to high risk; 3) an individual risk-factor strategy of treating only patients with LDL-C above a certain threshold; and 4) an age cutoff strategy of treating patients above an age when the average risk crosses from intermediate to high risk (i.e. a combination of strategies 1 and 2). An analysis of these 4 strategies (38) showed that the fourth strategy, based on the age cutoff, was a good compromise between high effectiveness and high efficiency in reducing CV events. The age transition from intermediate to high risk for CAD events of 47.9 years for men and 54.3 years for women is based on Canadian observations (2) and provides the basis for the recommendations for vascular protection.

OTHER RELEVANT GUIDELINES

Screening for the Presence of Coronary Artery Disease, p. S99
Vascular Protection in People With Diabetes, p. S102

Dyslipidemia, p. S107

Treatment of Hypertension, p. S115

Management of Acute Coronary Syndromes, p. S119

Treatment of Diabetes in People With Heart Failure, p. S123

RECOMMENDATIONS

1. Assessment for CAD risk should be performed periodically in people with diabetes and should include [Grade D, Consensus]:

- CV history (dyspnea, chest discomfort)
- Lifestyle (smoking, sedentary lifestyle, poor eating habits)
- Duration of diabetes
- Sexual function history
- Abdominal obesity
- Lipid profile
- Blood pressure
- Reduced pulses or bruits
- Glycemic control
- Presence of retinopathy
- Estimated glomerular filtration rate and random albumin to creatinine ratio
- Periodic electrocardiograms as indicated (see "Screening for the Presence of Coronary Artery Disease," p. S99).

2. The following individuals with diabetes should be considered at high risk for CV events:

- Men aged ≥ 45 years, women aged ≥ 50 years [Grade B, Level 2 (2)].
- Men < 45 years and women < 50 years with ≥ 1 of the following [Grade D, Consensus]:
 - Macrovascular disease (e.g. silent myocardial infarction or ischemia, evidence of peripheral arterial disease, carotid arterial disease or cerebrovascular disease)
 - Microvascular disease (especially nephropathy and retinopathy)
 - Multiple additional risk factors, especially with a family history of premature coronary or cerebrovascular disease in a first-degree relative
 - Extreme level of a single risk factor (e.g. LDL-C > 5.0 mmol/L, systolic BP > 180 mm Hg)
 - Duration of diabetes > 15 years with age > 30 years.

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Screening for the Presence of Coronary Artery Disease

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Paul Poirier MD PhD FRCPC FACC FAHA

KEY MESSAGES

- Compared to people without diabetes, people with diabetes (especially women) are at higher risk of developing heart disease, and at an earlier age. Unfortunately, a large proportion will have no symptoms before either a fatal or nonfatal myocardial infarction (MI). Hence, it is desirable to identify patients at high risk for vascular events, especially patients with established severe coronary artery disease (CAD).
- In individuals at high risk of CAD (based on age, gender, description of chest pain, history of prior MI and the presence of several other risk factors), exercise stress testing is useful for the assessment of prognosis.
- Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor) and vascular disease. For those unable to perform an exercise test, pharmacologic or nuclear stress imaging may be required.

INTRODUCTION

The majority (65 to 80%) of people with diabetes will die from heart disease (1,2). Compared to people without diabetes, people with diabetes (especially women) are at higher risk of developing heart disease, and at an earlier age. A high proportion of deaths occur in patients with no prior signs or symptoms of cardiovascular disease (CVD). Furthermore, people with diabetes have a high prevalence of silent myocardial ischemia, and almost one-third of myocardial infarctions (MIs) occur without recognized or typical symptoms (silent MIs) (3). The goals of screening are to improve life expectancy and quality of life by preventing MI and heart failure through the early detection of coronary artery disease (CAD).

STRESS TESTING

Exercise stress testing is useful in patients at high risk of CAD for the assessment of prognosis and the identification of individuals who may benefit from coronary artery revascularization to improve long-term survival. The most predictive clinical observation for CAD in the person with or without diabetes is a history of chest pain or discomfort, but these features will be absent in a significant number (20 to 50%) of people with diabetes (4-10). Clinical findings such as dyspnea on exertion, resting electrocardiogram (ECG) abnormalities

or multiple risk factors for atherosclerosis may also indicate the presence of CAD. Recognition of such features is of clinical importance, as the outcome of CAD events is worse in people with diabetes when shortness of breath is the primary symptom (4).

The presence of CAD risk factors and resting ECG abnormalities identify patients with diabetes at increased risk of important CAD and abnormal stress ECG or perfusion imaging results (11). A resting ECG at the time of diagnosis of diabetes also provides a baseline to which future ECGs can be compared. In patients considered to be at high risk for CAD, a repeat resting ECG may detect changes that result from silent MI and lead to earlier detection of critical CAD. There is evidence that early screening and intervention in people with diabetes and with silent ischemia is beneficial and may improve long-term survival (7,12). Screening with exercise ECG stress testing will find 3-vessel CAD in 13 to 15% of those with abnormal stress test findings (10,13) and lead to angiography with revascularization in 1 to 3% of asymptomatic individuals (10,13-15). The Definition of Ischemia in Asymptomatic Diabetes (DIAD) study (11) is prospectively investigating the value of routine adenosine stress myocardial perfusion scanning in asymptomatic patients with type 2 diabetes ≥ 55 years for the prevention of coronary events. The baseline study showed either perfusion defects or stress-induced ECG abnormalities in 22% of patients and large defects in 6%. In this study, multiple risk factors for CAD did not help to predict the patients with positive screening tests for CAD. Yet, a randomized pilot study on the impact of stress testing to screen for CAD in asymptomatic subjects with diabetes suggested a significant reduction in cardiac death and MI (16). Larger and adequately powered studies are necessary to support this provocative observation before clinical practice is changed. However, it is important to keep in mind that the goals of screening for CAD are to improve life expectancy and quality of life by preventing MI and heart failure through early detection.

The choice of initial stress test should be based on evaluation of the resting ECG, the individual's ability to exercise, and local expertise and technology. ECG abnormalities that limit the diagnostic accuracy of a stress ECG include resting ST depression (≥ 1 mm), left bundle branch block (LBBB) or right bundle branch block, an intraventricular conduction defect with a QRS duration >120 ms, ventricular paced

rhythm or pre-excitation. Individuals with these resting ECG findings should have a stress test with an imaging modality such as scintigraphic myocardial perfusion imaging or echocardiography.

The strongest and most consistent prognostic marker identified during exercise ECG stress testing is the person's maximum exercise capacity (4). Although exercise capacity is decreased in individuals with diabetes (17,18), it is still of prognostic importance (4). Silent ischemia is most likely to occur in individuals with diabetes who are older (mean age 65 years) and have elevated total cholesterol and proteinuria (14). An ECG with ST-T abnormalities at rest has been shown to be most predictive for silent ischemia (OR 9.27, 95% CI, 4.44-19.38) and the only significant predictor of silent ischemia in women (14). The relevance of ST-T abnormalities as a predictive factor for silent ischemia emphasizes the importance of recording a resting ECG in most individuals with type 2 diabetes. An abnormal ECG may indicate the need for further investigations and result in the earlier detection and treatment of CAD (14). An abnormal exercise ECG is associated with an annual CAD event rate of 2.1%, compared with 0.97% in subjects with normal exercise ECG (15). Myocardial ischemia (whether silent or symptomatic) detected during exercise stress testing in individuals with diabetes is associated with poorer long-term survival compared to individuals without diabetes (7). Silent MI is common (40%) in older asymptomatic people with type 2 diabetes, but is more frequent (65%) in those with diabetes who also have microalbuminuria (19). People with diabetes and silent ischemia have an annual event rate for CAD of 6.2% (50% of events were new-onset angina and 50% cardiac death or MIs) (20). Thus, silent MI is a prelude not only to symptomatic ischemia, but also to potentially fatal events. Also, it has been shown in a randomized trial in patients with silent ischemia (the vast majority of whom did not have diabetes) that long-term anti-ischemic drug therapy (~11 years follow-up) reduces cardiac events (cardiac death, nonfatal MI, acute coronary syndrome or revascularization) with preservation of ejection fraction (21).

Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor) and vascular disease in this population. Individuals who cannot adequately exercise on a stress test have a poorer prognosis than those who can, regardless of the reason for this incapacity. Perfusion imaging also provides important prognostic information. Myocardial perfusion imaging has similar predictive value for cardiac death and nonfatal MI in individuals with diabetes as in those without diabetes (22). For those unable to perform an exercise ECG stress test, pharmacologic stress imaging using dipyridamole, adenosine or dobutamine testing is required. Stress echocardiography and stress nuclear imaging have similar values for cardiac events in the general population (23), but no comparative data are

available for the person with diabetes. In a meta-analysis of perfusion imaging, an abnormal scan was predictive of future CAD events in subjects with and without diabetes. However, the cardiac event rate in individuals with diabetes was significantly greater than in those without diabetes (22). The choice of the optimal imaging modality to detect stress-induced MI is best determined by local availability and expertise. The utility of newer CAD diagnostic modalities such as computed tomography angiography, coronary artery calcium scoring and cardiac magnetic resonance imaging is currently unknown in terms of guiding management decisions in patients with type 2 diabetes (24).

RECOMMENDATIONS

1. In the following individuals, in addition to CAD risk assessment, a baseline resting ECG should be performed [Grade D, Consensus] in:

- All individuals >40 years of age
- All individuals with duration of diabetes >15 years
- All individuals (regardless of age) with hypertension, proteinuria, reduced pulses or vascular bruits

A repeat resting ECG should be performed every 2 years in people considered at high risk for CV events [Grade D, Consensus].

2. Persons with diabetes should undergo investigation for CAD by exercise ECG stress testing as the initial test [Grade D, Consensus] in the presence of the following:

- Typical or atypical cardiac symptoms (e.g. unexplained dyspnea, chest discomfort) [Grade C, Level 3 (4)]
- Resting abnormalities on ECG (e.g. Q waves) [Grade D, Consensus]
- Peripheral arterial disease (abnormal ankle-brachial ratio) [Grade D, Level 4 (9)]
- Carotid bruits [Grade D, Consensus]
- Transient ischemic attack [Grade D, Consensus]
- Stroke [Grade D, Consensus]

3. Pharmacologic stress echocardiography or nuclear imaging should be used in individuals with diabetes in whom resting ECG abnormalities preclude the use of exercise ECG stress testing (e.g. LBBB or ST-T abnormalities) [Grade D, Consensus]. In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging [Grade C, Level 3 (22)].

4. Individuals with diabetes who demonstrate ischemia at low exercise capacity (<5 metabolic equivalents [METs]) on stress testing should be referred to a cardiac specialist [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Identification of Individuals at High Risk of Coronary Events, p. S95

Vascular Protection in People With Diabetes, p. S102

Dyslipidemia, p. S107

Treatment of Hypertension, p. S115

Management of Acute Coronary Syndromes, p. S119
 Treatment of Diabetes in People With Heart Failure, p. S123

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Vascular Protection in People With Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The first priority in the prevention of macrovascular complications should be reduction of cardiovascular (CV) risk through a comprehensive, multifaceted approach, integrating both lifestyle and pharmacologic measures.
- Treatment with angiotensin-converting enzyme (ACE) inhibitors has been shown to result in better outcomes for people with atherosclerotic vascular disease, recent myocardial infarction, left ventricular impairment and heart failure. In a similar population, angiotensin II receptor antagonists have been shown to be noninferior to ACE inhibitors for vascular protection.
- Low-dose acetylsalicylic acid therapy may be considered in people with stable CVD. The decision to prescribe antiplatelet therapy for primary prevention of CV events, however, should be based on individual clinical judgment.

VASCULAR PROTECTION

In order to reduce the excessive cardiovascular disease (CVD) risk associated with diabetes, all coronary risk factors must be addressed and treated aggressively. The Steno-2 studies (1,2) demonstrated that a target-driven, comprehensive, multifaceted approach to risk factor management applied to high-risk patients with type 2 diabetes and microalbuminuria over a period of 7 years resulted in a >50% reduction of CVD (HR 0.47, 95% CI, 0.24–0.73)

and microvascular events (nephropathy HR 0.39, 95% CI, 0.17–0.87; retinopathy HR 0.42, 95% CI, 0.21–0.86). It is likely that similar relative benefits would be achieved by applying a comprehensive, multifaceted approach to risk factor control in high-risk patients with diabetes who do not have microalbuminuria.

Patients at the highest risk for CV events include those who have diabetes and atherosclerotic vascular disease that includes either clinically recognized disease (e.g. coronary artery disease [CAD], peripheral arterial disease [PAD] and cerebrovascular disease) or clinically silent disease (e.g. silent myocardial ischemia or infarction, and PAD identified by the presence of bruits or abnormal ultrasound or ankle-brachial index). Other patients at high risk include those with microvascular disease and multiple risk factors or extreme levels of a single risk factor (Table 1) (see also "Identification of Individuals at High Risk of Coronary Events," p. S95).

When deciding on appropriate treatment strategies, it is important to prioritize treatment goals. Since some of the available treatments, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs), have potential uses in controlling blood pressure (BP) as well as reducing the risks for CVD and nephropathy, it can be challenging to integrate the data to make recommendations for one application over another. Table 2 summarizes the priorities for vascular and renal protection, while Table 3 summarizes recommended interventions for vascular protection.

Table 1. People with diabetes considered at high risk of a CV event*

- Men aged ≥ 45 years, women aged ≥ 50 years
- Men <45 years and women <50 years with ≥ 1 of the following:
 - Macrovascular disease (MI or ischemia, CAD, PAD, stroke, transient ischemic attack, cerebrovascular disease, evidence of silent MI or ischemia or PAD)
 - Microvascular disease (especially nephropathy or retinopathy)
 - Multiple additional risk factors, especially with a family history of premature coronary or cerebrovascular disease in a first-degree relative
 - Extreme level of a single risk factor (e.g. LDL-C >5.0 mmol/L, systolic BP >180 mm Hg)
 - Duration of diabetes >15 years with age >30 years

*See also "Identification of Individuals at High Risk of Coronary Events," p. S95

BP = blood pressure
CAD = coronary artery disease
CV = cardiovascular

LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
PAD = peripheral arterial disease

Table 2. Priorities for vascular and renal protection

Clinical strategy	Target population
Step 1: Initiate vascular protection	All people with diabetes (see Table 3)
Step 2: Treat elevated BP	All people with diabetes whose BP remains $\geq 130/80$ mm Hg after applying vascular protective measures (see "Treatment of Hypertension," p. S115)
Step 3: Initiate renal protection	All people with diabetes who have proteinuria after applying vascular measures and after achieving BP $< 130/80$ mm Hg (See "Chronic Kidney Disease in Diabetes," p. S126)

BP = blood pressure

Table 3. Interventions for vascular protection

Population	Interventions (in alphabetical order)
All people with diabetes	<ul style="list-style-type: none"> • Lifestyle modifications <ul style="list-style-type: none"> • Achievement and maintenance of a healthy body weight (see "Management of Obesity in Diabetes," p. S77) • Healthy diet (see "Nutrition Therapy," p. S40) • Regular physical activity (see "Physical Activity and Diabetes," p. S37) • Smoking cessation • Optimize BP control (see "Treatment of Hypertension," p. S115) • Optimize glycemic control (see "Targets for Glycemic Control," p. S29)
People with diabetes considered at high risk of a CV event (see Table 1)	<ul style="list-style-type: none"> • ACE inhibitor or ARB therapy (see Recommendation #2) • Antiplatelet therapy (see Recommendation #3) • Lipid-lowering medication (primarily statins) (see "Dyslipidemia," p. S107)

ACE = angiotensin converting enzyme

ARB = angiotensin II receptor antagonist

BP = blood pressure

CV = cardiovascular

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITION

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathophysiology of vascular and cardiac disease, especially in people with diabetes. Interruption of the RAAS with ACE inhibitors has been shown to result in better outcomes for people with atherosclerotic vascular disease, recent myocardial infarction (MI), left ventricular (LV) impairment and heart failure.

The Heart Outcomes Prevention Evaluation (HOPE) study (3) examined the hypothesis that ACE inhibitors would reduce the incidence of acute vascular events (CV mortality, nonfatal MI and stroke) in individuals at high risk. Subjects included in the HOPE trial were >55 years of age and had proven coronary disease, cerebrovascular disease or PAD, or diabetes plus ≥ 1 additional risk factor for vascular disease. In the overall population, ramipril 10 mg daily reduced the primary endpoint by 22% ($p < 0.001$), with a significant reduction of each of its components (CV death 26% [$p < 0.001$], nonfatal MI 20% [$p < 0.001$] and stroke 32% [$p < 0.001$]). The MICRO-HOPE analysis (4) of the 38% of subjects in the HOPE study with diabetes ($n = 3577$) showed an enhanced benefit from ramipril in this population. CV death was reduced by 37% ($p < 0.0001$), MI by 22% ($p < 0.01$) and stroke by 33% ($p < 0.0074$). The subgroup of 2458 subjects with diabetes and CVD had a significant reduction of the primary outcome. In the subgroup of 1119 subjects with diabetes and no established CVD, the reduction of the primary endpoint did not achieve significance. Other benefits observed in the MICRO-HOPE trial included a reduced progression of nephropathy and reduced development of heart failure.

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study (5) included 12 218 subjects with CAD (prior MI, history of revascularization, angiographically proven coronary disease with $>70\%$ stenosis and chest pain with abnormal stress testing). Treatment with perindopril 8 mg daily resulted in a significant 20% reduction of the primary composite endpoint of CV mortality, resuscitated cardiac arrest and nonfatal MI ($p < 0.0003$). In the 1502 subjects with diabetes enrolled in the EUROPA study (6), the benefits from perindopril were similar to those observed in the overall group; however, the sample size was too small to show a statistically significant benefit in this subgroup.

The Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE) study (7) randomized 8290 subjects with stable CAD and normal or mildly impaired LV function to receive either trandolapril 4 mg daily or placebo. A modified primary endpoint of CV death, nonfatal MI and coronary revascularization was not significantly reduced (HR 0.96, 95% CI, 0.88–1.06) during the median follow-up period of 4.8 years. The majority of endpoints were due to coronary revascularization, which was not modified by ACE inhibition.

A combined analysis (8) of the 3 trials (HOPE, EUROPA and PEACE) showed that all-cause mortality, CV mortality, nonfatal MI, all stroke, congestive heart failure and revascularization by coronary bypass surgery, but not percutaneous coronary intervention, were reduced by ACE inhibition treatment. The combined endpoint of CV death, nonfatal MI and stroke was reduced by 18% (OR 0.82, 95% CI, 0.76–0.88). A meta-analysis (9) of 7 studies of ACE inhibition in people with CAD or diabetes plus 1 additional risk factor treated for

at least 2 years showed decreased overall mortality (OR 0.86, 95% CI, 0.79–0.93), CV mortality (OR 0.81, 95% CI, 0.73–0.90), MI (OR 0.82, 95% CI, 0.75–0.89) and stroke (OR 0.77, 95% CI, 0.66–0.88).

Whether the benefits of ACE inhibition result from a reduction of BP remains controversial. The benefits of ACE inhibition in both the HOPE and EUROPA trials were observed in individuals with or without a history of hypertension, and in those with higher and lower BP readings (4,5). Furthermore, recent analyses of BP trials have indicated a benefit of ACE inhibition beyond that of BP lowering (10). Also, trials of other agents such as calcium channel blockers, which lower BP in normotensive individuals with CAD, have failed to reduce coronary events other than those related to a reduction of angina (11).

The HOPE and EUROPA studies confirmed the benefit of ACE inhibition in people with diabetes and established vascular disease (4,5). The HOPE study is the only study that has included individuals with diabetes and no evident vascular disease. In this relatively small subgroup, the point estimate of benefit was of similar magnitude to the overall group, yet did not achieve significant benefit. Hence, the level of evidence and the recommendation are less robust for this population than for people with both diabetes and CVD.

ARBs have been shown to be noninferior to ACE inhibition for the prevention of events in patients with heart failure and in those with reduced LV ejection fraction after MI. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study (12) compared the vascular protective properties of the ACE inhibitor ramipril with the ARB telmisartan and the combination of the ACE and the ARB in patients at high risk for vascular events. Of the 25 620 patients entered in the study, 9632 had diabetes. Of these patients, 7406 had diabetes and vascular disease, and 2226 had “high-risk diabetes.” The ONTARGET patients with “high-risk diabetes” (defined as diabetes with non-macrovacular end-organ damage [i.e. with diabetic nephropathy or retinopathy]) were different from the HOPE patients (diabetes with ≥ 1 CV risk factors). In the overall study, telmisartan 80 mg daily was noninferior to ramipril 10 mg daily for the primary endpoint of death, MI, stroke and admission to hospital with heart failure, when administered for a median period of 56 months (RR 1.01, 95% CI, 0.94–1.09). The telmisartan-treated patients had less cough and angioedema, but more hypotensive episodes. The combination of ramipril and telmisartan was not superior to ramipril alone, and hypotensive adverse effects, including syncope were more frequent in the dual-treatment arm. For patients with diabetes, the primary end-point relative risk point estimate was close to 1 and similar to the group without diabetes, both for those receiving telmisartan compared to ramipril, as well as for those receiving the combination of telmisartan and ramipril compared to ramipril alone. For patients with diabetes and nonvascular end-organ dam-

age, the point estimate was also close to 1, however due to the small sample size the confidence intervals were wide. In summary, for patients with diabetes with vascular disease, the ARB telmisartan was not inferior to ramipril to prevent vascular events, however no confidence intervals or noninferiority margins for this population have yet been published. For patients with diabetes and nonvascular end-organ damage the sample size is too small to make any conclusive recommendation.

ANTIPLATELET THERAPY

In addition to traditional risk factors for CVD such as smoking, hypertension, hyperglycemia and dyslipidemia, atherosclerosis in people with diabetes can be accelerated by a procoagulant state. Individuals with diabetes have a variety of alterations in platelet function that can predispose them to increased platelet activation and thrombosis, including increased turnover (13), enhanced aggregation (14) and increased thromboxane synthesis (15). The efficacy of antiplatelet agents in people with diabetes also appears to be reduced, particularly in those with poor metabolic control (16,17).

Acetylsalicylic acid (ASA) is the antiplatelet agent most commonly studied in the prevention of CV events in people with diabetes. A number of primary, mixed primary/secondary, and secondary CV event prevention trials have studied the effect of ASA in diabetes with varied results. The US Physicians Health Study (18) was a primary prevention trial with a subgroup of 533 male physicians with diabetes treated with 325 mg ASA every 2 days. ASA use reduced the risk of MI by 60%, although the results were not significant due to the small number of events (11/275 in the ASA group vs. 26/258 in the placebo group, $p=0.22$). The Primary Prevention Project (PPP) trial (19) studied the effect of low-dose ASA (100 mg/day) in over 1000 people with diabetes and found a marginal decrease in major CV events (RR 0.90, 95% CI, 0.50–1.62) with a nonsignificant 23% increase in CV deaths. This result is in contrast to the significant 41% reduction in major CV events seen in individuals without diabetes. The Hypertension Optimal Treatment (HOT) (20) trial studied the effect of 75 mg ASA daily in a subset of 1501 high-risk subjects with diabetes and hypertension. Fewer than 10% of subjects had clinical evidence of previous MI, stroke or other CAD. In the whole HOT population, ASA reduced the risk of pooled CV events by 15% and the risk of MI by 36%. Specific data on the diabetes subgroup were not included, but the subjects with diabetes and CVD were reported to have had similar outcomes to the overall HOT population.

The Antithrombotic Trialists (21) reported a meta-analysis of 195 randomized trials of antiplatelet therapy published up to 1997, including 9 trials with almost 5000 people with diabetes. Compared to a 22% reduction in the risk of major CV events among all 140 000 high-risk subjects on antiplatelet therapy, subjects with diabetes showed no significant benefit

(7±8% risk reduction). Within this meta-analysis, the Early Treatment Diabetic Retinopathy Study (ETDRS) (22) was the only trial specifically designed to examine the effect of high-dose ASA in high-risk subjects with diabetes and retinopathy. The reduction in serious vascular events (vascular death, non-fatal MI, nonfatal stroke) was nonsignificant (RR 0.91, 99% CI, 0.75–1.11), although a larger reduction (although still nonsignificant) was noted for fatal and nonfatal MI (RR 0.83, 99% CI, 0.66–1.04).

Taken together, these studies suggest that ASA therapy may confer less benefit for CV event reduction in individuals with diabetes than in those without diabetes. This may be due to increased ASA resistance in people with diabetes, as well as ASA-insensitive mechanisms of platelet activation and thrombus formation. Given the known benefit of ASA in secondary prevention of vascular events in the general population (21) and a trend toward MI reduction in people with diabetes and CAD (22), it is reasonable to consider prescribing ASA for people with diabetes and CAD. The decision to prescribe ASA for primary prevention of CV events should be based on individual clinical judgment given the lack of evidence for benefit and the side effects of long-term use.

If an antiplatelet agent is to be used, ASA appears to be as effective as other antiplatelet agents (20) and may be the best choice given that it is the most widely studied and the most economical. Patients who cannot tolerate ASA should substitute an alternate antiplatelet agent, such as clopidogrel. Clopidogrel is an inhibitor of adenosine diphosphate-induced platelet aggregation that is effective for secondary prevention in people with diabetes. In the posthoc analysis of the diabetic subgroup (1914 patients) of the Clopidogrel Versus Aspirin in Patients with Risk of Ischemic Events (CAPRIE) trial, the composite vascular endpoint (ischemic stroke, MI or vascular death) occurred in 15.6% of those randomized to daily treatment with 75 mg clopidogrel vs. 17.7% of those on 325 mg of ASA ($p=0.42$) (23). The addition of clopidogrel to low-dose ASA was not shown to be of benefit in high-risk subjects with diabetes in the Clopidogrel and Aspirin Versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial (24).

The effective dose of ASA in people with diabetes remains controversial. It has been suggested that due to the increase in platelet turnover and thromboxane synthesis in diabetes, higher doses or multiple daily dosing of ASA may be preferred (16). Clinical trials in subjects without diabetes suggest no differences in daily ASA dosages in terms of reducing CV risk. Similar results were seen in both the ETDRS and the PPP trials, despite the use of 650 mg per day in the former and 100 mg per day in the latter. There have been no clinical trials on whether multiple daily dosing would improve CV outcomes. Low-dose ASA (75–325 mg daily) is often recommended to limit both gastrointestinal (GI) toxicity and the potential adverse effects of prostaglandin inhibition on renal function or BP control.

ASA therapy does not increase the risk of vitreous hemorrhage in people with diabetic retinopathy (17), nor does it increase stroke or fatal bleeds in those with adequately controlled hypertension (18). Antiplatelet agents should not be used in people with inherited or acquired bleeding disorders, recent GI bleeding or serious hepatic failure. ASA should not be used in individuals <21 years of age because of the risk of Reye syndrome.

RECOMMENDATIONS

1. The first priority in the prevention of diabetes complications should be the reduction of CV risk by vascular protection through a comprehensive, multifaceted approach [*Grade D, Consensus, for all people with diabetes; Grade A, Level 1A (1), for people with type 2 diabetes age >40 years with microalbuminuria*] as follows:

- For all people with diabetes (in alphabetical order):
 - Lifestyle modification
 - Achievement and maintenance of a healthy body weight
 - Healthy diet
 - Regular physical activity
 - Smoking cessation
 - Optimize BP control
 - Optimize glycemic control
- For all people with diabetes considered at *high risk* of a CV event (in alphabetical order):
 - ACE inhibitor or ARB therapy
 - Antiplatelet therapy (as recommended)
 - Lipid-lowering medication (primarily statins)

2. Individuals with diabetes at high risk for CV events should receive an ACE inhibitor or ARB at doses that have demonstrated vascular protection [*Grade A, Level 1A, for people with vascular disease (4,12); Grade B, Level 1A, for other high-risk groups (4,12)*].

3. Low-dose ASA therapy (81–325 mg) may be considered in people with stable CVD [*Grade D, Consensus*]. Clopidogrel (75 mg) may be considered in people unable to tolerate ASA [*Grade D, Consensus*]. The decision to prescribe antiplatelet therapy for primary prevention of CV events, however, should be based on individual clinical judgment [*Grade D, Consensus*].

OTHER RELEVANT GUIDELINES

Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories, p. S10

Screening for Type 1 and Type 2 Diabetes, p. S14

Targets for Glycemic Control, p. S29

Physical Activity and Diabetes, p. S37

Nutrition Therapy, p. S40

Management of Obesity in Diabetes, p. S77

Identification of Individuals at High Risk of Coronary Events, p. S95

Screening for the Presence of Coronary Artery Disease, p. S99

Dyslipidemia, p. S107

Treatment of Hypertension, p. S115

Management of Acute Coronary Syndromes, p. S119
 Treatment of Diabetes in People With Heart Failure, p. S123

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Dyslipidemia

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The beneficial effects of lowering low-density lipoprotein (LDL-C) with statin therapy apply equally well to people with diabetes as to those without.
- The primary target for most people with diabetes is an LDL-C of ≤ 2.0 mmol/L, which is generally achievable with statin monotherapy.
- The secondary goal is a total cholesterol/high-density lipoprotein cholesterol ratio of < 4.0 . This is often more difficult to achieve than the primary LDL-C target, and may require improved glycemic control, intensification of lifestyle changes (weight loss, physical activity, smoking cessation) and, if necessary, pharmacologic interventions.

DYSLIPIDEMIA IN DIABETES

Diabetes is associated with a high risk of vascular disease (2- to 4-fold greater than that of individuals without diabetes), with cardiovascular disease (CVD) being the primary cause of death among people with type 1 or type 2 diabetes (1-3). Aggressive management of all CV risk factors, including dyslipidemia, is therefore generally necessary (4). The most common lipid pattern in people with type 2 diabetes consists of hypertriglyceridemia (hyper-TG), low high-density lipoprotein cholesterol (HDL-C) and normal plasma concentrations of low-density lipoprotein cholesterol (LDL-C). However, in the presence of even mild hyper-TG, LDL-C particles are typically small and dense and may be more susceptible to oxidation. In addition, chronic hyperglycemia promotes the glycation of LDL-C, and both these processes are believed to increase the atherogenicity of LDL-C. In those with type 1 diabetes, plasma lipid and lipoprotein concentrations may be normal, but there may be oxidation and glycation of the lipoproteins, which may impair their function and/or enhance their atherogenicity.

RISK ASSESSMENT OF INDIVIDUALS WITH DIABETES

People with diabetes should be assessed to determine their short- and long-term risks for CVD. Most individuals with established diabetes are at high risk for vascular events and should be treated accordingly. Clinical assessment can identify those with diabetes whose risk level might be considered

lower, but even in this group, it is important to consider that the average person with newly diagnosed type 2 diabetes may have had the disease for some time prior to diagnosis. In addition, all people with diabetes have an extremely high lifetime risk of CVD; thus, even if the short-term risk is lower, early intervention to improve the lipid profile may be warranted. Physicians must also use their clinical judgement and carefully weigh diabetes-specific as well as traditional CVD risk factors in their decisions about when and how to implement risk-reduction strategies in a given individual (see "Identification of Individuals at High Risk of Coronary Events," p. S95).

SCREENING

The burden of dyslipidemia is high in people with diabetes. A national cross-sectional chart audit study of 2473 Canadians with type 2 diabetes revealed that 55% of those with a diagnosis of diabetes of ≤ 2 years had dyslipidemia. This proportion rose to 66% in those with diabetes for ≥ 15 years (5). A fasting lipid profile (total cholesterol [TC], HDL-C, TG and calculated LDL-C) should therefore be conducted at the time of diagnosis of diabetes, and then every 1 to 3 years, as clinically indicated. More frequent testing should be conducted if treatment for dyslipidemia is initiated. A fast of > 8 hours may be inappropriate for individuals with diabetes, especially if they are using a long-acting insulin. For screening in children and adolescents, please refer to the diabetes in children sections, pages S150 and S162.

LIFESTYLE MODIFICATION

Lifestyle interventions remain a key component of CVD prevention strategies and diabetes management in general. Individuals with type 2 diabetes are frequently overweight and sedentary. In those with a body mass index (BMI) ≥ 25 kg/m² and/or abdominal obesity (6), weight reduction should be strongly recommended. Even a modest weight loss of 5 to 10% of initial body weight can be associated with an improvement in the lipid profile of individuals with dyslipidemia and diabetes (7). As well, an energy-restricted, well-balanced diet that is low in dietary cholesterol, saturated fats, trans fatty acids and refined carbohydrates is essential. In short-term studies, a combination of various dietary interventions (increased intake of viscous fibres, plant sterols, nuts and soy proteins) was shown to lower LDL-C by 30% in

highly motivated individuals with hypercholesterolemia but without diabetes (8). However, in a “real-world” setting, only one-third of individuals were able to adhere to this diet over a 1-year period of time (9). Regular aerobic exercise helps individuals lose weight and maintain this weight reduction over time (10), and may be associated with reductions in TG and elevations in HDL-C. Regular exercise can also improve glycemic control in people with type 2 diabetes (11) and is associated with substantial reductions in CV morbidity and mortality in both type 1 (12) and type 2 diabetes (13-15). Indeed, a steep inverse relationship between fitness and mortality was observed in a cohort of men with diabetes, and this association was independent of BMI (16). Smoking cessation should be encouraged and supported. While lifestyle modification should be encouraged in all people with dyslipidemia, most will be unable to achieve recommended lipid targets without pharmacologic intervention. Accordingly, for most people with diabetes, lifestyle interventions should be seen as an important adjunct to, but not a substitute for, pharmacologic treatment.

LDL-C

A number of studies have shown that the degree of LDL-C lowering with statins and the beneficial effects of lowering LDL-C apply equally well to people with and without diabetes (17-24). Large, recently published trials have demonstrated the benefits of statin therapy in both the primary and secondary prevention of vascular disease, and subgroup analyses of these studies have shown similar benefits in subsets of participants with diabetes (17-19). While statin therapy across all subgroups has shown the same relative risk reduction in terms of outcomes, the absolute benefit depends on absolute risk, which is increased in people with diabetes. Subgroup analyses from statin trials have also shown similar benefits of LDL-C lowering, regardless of baseline LDL-C (20,22). Therefore, statin use should be considered for any person with diabetes at high risk of a vascular event. In the very small group of lower-risk individuals with type 2 diabetes, the relative reduction in CVD risk with statin therapy is likely to be similar to those at higher global risk for CVD, but the absolute benefit from statin therapy is predicted to be small. However, such individuals' global CVD risk will increase with age and in the presence of additional risk factors for CVD. Therefore, repeated monitoring of the individual's clinical condition and lipid screening every 1 to 3 years, as outlined in the Screening section above, are recommended.

The results of the Heart Protection Study (HPS) provide considerable insight into the importance of LDL-C lowering (21). In this large study involving >20 000 subjects, a similar benefit in terms of risk ratio reduction was observed in subjects with baseline LDL-C >3.5 mmol/L, 3.0 to 3.5 mmol/L and <3.0 mmol/L. All randomized subjects were included in this analysis. In the cohort with diabetes (n=5963, including

615 people with type 1 diabetes), treatment with 40 mg simvastatin daily resulted in a 27% reduction in CV events and a 25% reduction in stroke relative to treatment with placebo. The risk reduction was similar in the cohorts with and without diabetes, and the treatment benefit was independent of baseline HDL-C and LDL-C levels (LDL-C <3.0 mmol/L or \geq 3.0 mmol/L), sex, vascular disease, type of diabetes (type 1 vs. type 2) and glycated hemoglobin (A1C) (20). These results confirmed that whatever the existing serum LDL-C level, lowering it further with the use of a statin is beneficial. However, the HPS did not demonstrate the effect of treating LDL-C to any particular preset targets. In a post-hoc analysis of the entire study sample, the investigators found similar event reductions in individuals with baseline LDL-C values <2.6 mmol/L, but this analysis was not performed in the subset of people with diabetes who had baseline LDL-C values <2.6 mmol/L because of insufficient power.

In the Collaborative Atorvastatin Diabetes Study (CARDS) (22), the first completed statin trial to be conducted exclusively in people with type 2 diabetes without known vascular disease, mean baseline LDL-C was 3.1 mmol/L, and all subjects had at least 1 additional CV risk factor (i.e. in addition to known diabetes). CARDS demonstrated that treatment with atorvastatin 10 mg daily was safe and highly efficacious in reducing the risk of first CVD events, including stroke. Treatment resulted in a mean LDL-C of 2.0 mmol/L and was associated with a 37% reduced risk for CV events and a 48% reduced risk for stroke. The study provided important new evidence to support the value of treating even so-called “normal” LDL-C levels in people with type 2 diabetes and no known vascular disease. CARDS subjects all had at least 1 additional CV risk factor – a profile that would also apply to an estimated 70 (25) to 80% (22) of people with type 2 diabetes; analysis of the United States (US) Third National Health and Nutrition Examination Survey (NHANES III) data indicates that 82% of people with diabetes and no clinically evident coronary artery disease (CAD) have at least 1 of the CARDS entry criteria risk factors (22). The authors of CARDS conclude that the data “challenge the use of a particular threshold level of LDL-C as the sole arbiter of which individuals with type 2 diabetes should receive statin therapy ... The absolute risk, determined by other risk factors in addition to LDL-C, should drive the target levels.” Indeed, the authors question whether any individuals with type 2 diabetes can be considered at sufficiently low risk for statin therapy to be withheld (22). A recently published subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) revealed similar benefits of atorvastatin 10 mg vs. placebo in people with type 2 diabetes, hypertension and at least 3 additional risk factors (26).

The Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) (27) assessed the effect of 10 mg atorvastatin vs. placebo on CVD prevention in 2410 people with

type 2 diabetes. Although originally designed as a secondary prevention trial, the protocol underwent several changes, including the addition of subjects without known CAD, and the eventual switch of all patients with known CAD to open-label lipid-lowering medication. Mean LDL-C reduction over 4 years in the atorvastatin group was 29% vs. placebo ($p < 0.0001$). The composite primary endpoint was reduced by a nonsignificant 13.7%, which is generally believed to be related to the methodological limitations of the study design and the protocol changes.

In the diabetic subset ($n=1051$) of the Treating to New Targets (TNT) trial (24) conducted in individuals with stable CAD, those subjects treated with atorvastatin 80 mg daily who achieved a group mean LDL-C of 2.0 mmol/L had 25% fewer major CV events than those treated with atorvastatin 10 mg daily who achieved a mean LDL-C of 2.5 mmol/L ($p=0.026$). Intensive therapy with atorvastatin 80 mg vs. therapy with 10 mg also reduced the rate of all CV and cerebrovascular events. Notably, an increased event rate for all primary and secondary efficacy outcomes was noted for the diabetes subgroup compared with the overall study population, reinforcing the evidence that people with diabetes and CAD have an extremely high risk of subsequent CV events.

A recent meta-analysis of >90 000 statin-treated subjects indicated that for every 1.0 mmol/L reduction in LDL-C there was an approximately 20% reduction in CVD events, regardless of baseline LDL-C. The proportional reductions were very similar in all subgroups, including those with diabetes without pre-existing vascular disease (28). Although this linear relationship between the proportional CVD risk reduction and LDL-C lowering would suggest that there is no lower limit of LDL-C or specified LDL-C target (as the authors suggest), the clinical trial evidence summarized above would suggest that a target LDL-C of ≤ 2.0 mmol/L is currently the most appropriate target for high-risk individuals. This target is achievable in the vast majority of people with either a statin alone or a statin in combination with a second agent, such as a cholesterol absorption inhibitor. For those with an on-treatment LDL-C of 2.0 to 2.5 mmol/L, the physician should use clinical judgement as to whether additional LDL-C lowering is required.

Table 1 summarizes recommended treatment targets. Tables 2A and 2B summarize considerations that should guide the choice of pharmacologic agent(s) to treat dyslipidemia.

People with impaired glucose tolerance (IGT) (particularly in the context of the metabolic syndrome) are at significant risk for the development of CVD. Indeed, some studies suggest that their vascular risk is almost as high as individuals with type 2 diabetes (29). No clinical trial of lipid-lowering agents has been conducted exclusively in people with IGT; however, given their increased CV risk, one can consider treating this population to the same targets as people with diabetes (30). To reduce the CV morbidity

Table 1. Lipid targets for individuals with diabetes at high risk for CVD

Index	Target value
Primary target: LDL-C	≤ 2.0 mmol/L*
Secondary target: TC/HDL-C ratio	<4.0

*Clinical judgement should be used to decide whether additional LDL-C lowering is required for individuals with an on-treatment LDL-C of 2.0 to 2.5 mmol/L

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

TC = total cholesterol

Table 2A. First-line therapy to achieve primary lipid target of LDL-C ≤ 2.0 mmol/L

Statins*		
Generic name [†]	Trade name	Considerations
atorvastatin	Lipitor	Drugs of choice to lower LDL-C. At higher doses, modest TG-lowering effects and HDL-C-raising effects
fluvastatin	Lescol	
lovastatin	Mevacor and generic	
pravastatin	Pravachol and generic	
rosuvastatin	Crestor	
simvastatin	Zocor and generic	

*Prevention of statin-induced myopathy requires attention to factors that increase risk, such as age >80 years (especially women); small body frame and frailty; higher dose of statin; multisystem diseases (e.g. chronic renal insufficiency due to diabetes); multiple medications; hypothyroidism; perioperative periods; alcohol abuse; excessive grapefruit juice consumption; and specific concomitant medications such as fibrates (especially gemfibrozil) (refer to specific statin package inserts for others) (47)

[†]Listed in alphabetical order

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

TG = triglyceride

Note: Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

Table 2B. Other lipid-modifying medications

Drug class* Generic name* (trade name)	Principal effects	Other considerations
Bile acid sequestrants <ul style="list-style-type: none"> cholestyramine resin (Questran, Questran Light and generic) colestipol HCl (Colestid) 	<ul style="list-style-type: none"> Lower LDL-C 	<ul style="list-style-type: none"> GI intolerance, which worsens with increasing doses May elevate TG
Cholesterol absorption inhibitor <ul style="list-style-type: none"> ezetimibe (Ezetrol) 	<ul style="list-style-type: none"> Lower LDL-C 	<ul style="list-style-type: none"> Less effective than statins as monotherapy Effective when used in combination with a statin to further lower LDL-C
Fibrates <ul style="list-style-type: none"> bezafibrate (Bezalip and generic) fenofibrate (micronized/microcoated) (Lipidil Micro/Lipidil Supra, Lipidil EZ and generic) gemfibrozil (Lopid and generic) 	<ul style="list-style-type: none"> Lower TG Variable effect on LDL-C Highly variable effect on HDL-C (more effective at raising HDL-C when baseline TG is high) 	<ul style="list-style-type: none"> May also increase creatinine and homocysteine levels Do not use gemfibrozil in combination with a statin due to increased risk of myopathy and rhabdomyolysis[†]
Nicotinic acid <ul style="list-style-type: none"> Extended-release niacin (Niaspan) Immediate-release niacin (generic, non-prescription) Long-acting (e.g. "no-flush") niacin (generic, nonprescription) Not recommended 	<ul style="list-style-type: none"> Raise HDL-C Lower TG Lower LDL-C 	<ul style="list-style-type: none"> Can cause dose-related deterioration of glycemic control Extended-release niacin has similar efficacy and better tolerability than immediate-release niacin Long-acting niacin should not be used due to increased hepatotoxicity and decreased efficacy (52)

*Listed in alphabetical order

[†]See footnote to Table 2A regarding prevention of myopathy

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

TG = triglyceride

Note: Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

and mortality associated with prediabetes and metabolic syndrome, an aggressive approach aimed at associated CV risk factors, including dyslipidemia, is warranted. Lifestyle interventions aimed at reducing the risk of developing both type 2 diabetes and coronary disease are essential.

TC/HDL-C RATIO, HDL-C, TG

The TC/HDL-C ratio is a sensitive and specific index of CV risk (31). This simple lipid ratio is recommended as a secondary goal of therapy. Once the LDL-C goal of ≤ 2.0 mmol/L has been reached, one can consider lowering the TC/HDL-C ratio to the recommended goal of < 4.0 (Table 1). This is typically more difficult to achieve than the primary LDL-C target, requires ongoing reinforcement of lifestyle modification and frequently requires combination therapy. Even with such aggressive measures, this secondary target is fre-

quently not achieved.

An elevated TC/HDL-C ratio in the face of an optimal LDL-C of ≤ 2.0 mmol/L is usually associated with a low HDL-C and/or elevated TG. This form of dyslipidemia is more amenable to lifestyle modification (increase in physical activity and weight reduction) and improvement in glycemic control than an isolated LDL-C elevation. Initially, treatment should consist of intensification of lifestyle modification and improvement of glycemic control, using glucose-lowering therapies as needed. If the ratio remains elevated after a 4- to 6-month trial of these measures, and once glycemic control and LDL-C have been optimized, adjuvant lipid-modifying therapy may be used in conjunction with statin therapy.

If low HDL-C is the major cause of a persistently elevated TC/HDL-C ratio (in those whose LDL-C is already opti-

mally controlled with a statin), niacin (immediate-release or extended-release formulation) is the adjuvant agent of choice. Combination lipid-lowering therapy with niacin is generally safe (32-35). Niacin can cause deterioration of glycemic control (32) (although there is now evidence that the adverse effects of niacin on glycemia may have been overemphasized [33]).

In the placebo-controlled HDL Atherosclerosis Treatment Study (HATS) (34), combined low-dose simvastatin (10 to 20 mg/day) and high-dose niacin (2 to 4 g/day) stabilized coronary atherosclerosis with an associated $\geq 13\%$ absolute risk reduction (up to 90% relative risk reduction) for CV outcomes, although the number of subjects with diabetes was small. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 trial, 1 g extended-release niacin added to existing statin therapy significantly improved HDL-C (21%), TG and non-HDL-C, and likely contributed to observed reduction of carotid intima-media thickness in subjects also treated with a statin (35).

Specific targets for TG are not provided in these guidelines because there are very few clinical trial data to support recommendations based on specific TG target levels. Nonetheless, a TG level of < 1.5 mmol/L is considered optimal, since below this level of hyper-TG there are fewer associated metabolic abnormalities such as low HDL-C, small dense LDL particles and postprandial lipemia (36,37). Recognizing the atherogenicity of small, dense LDL particles and remnant lipoproteins and the important antiatherogenic role of HDL particles, it is important to improve these metabolic parameters by lifestyle modification, improvement in glycemic control and pharmacotherapy when indicated. The atherogenic impact of LDL-C particle size will be minimized and reductions in TC/HDL-C ratio will occur if very low plasma concentrations of LDL-C are achieved.

To reduce the risk of pancreatitis, a fibrate is recommended for individuals with fasting TG levels > 10.0 mmol/L who do not respond to other measures such as tight glycemic control, weight loss and restriction of refined carbohydrates and alcohol. For those with moderate hyper-TG (4.5 to 10.0 mmol/L), either a statin or a fibrate can be attempted as first-line therapy, with the addition of a second lipid-lowering agent of a different class if target lipid levels are not achieved after 4 to 6 months on monotherapy. While several studies have shown that CVD prevention is associated with fibrate treatment (38-42), there is much less evidence for CVD risk reduction with fibrates relative to statins in people with diabetes. In some studies, no statistically significant reduction in the primary endpoint was demonstrated with fibrate therapy (43,44). Combination therapy with fenofibrate (45,46) or bezafibrate plus a statin appears to be relatively safe if appropriate precautions are taken (Tables 2A and 2B), but the efficacy of these approaches with regard to outcomes has yet to be established. Because of an increased risk

of myopathy and rhabdomyolysis, statins should not be used in combination with gemfibrozil (47).

Although monotherapy with niacin or fibrates has been shown to prevent CVD events, there is currently insufficient evidence for statin plus niacin and no evidence for fibrate plus niacin combinations to reduce CV risk in people with diabetes. However, adequately powered, event-reduction, prospective, randomized, controlled clinical trials are currently underway with various classes of agents to examine whether the addition of other therapies in individuals already treated with statins further reduces CV events and/or prolongs survival (Action to Control Cardiovascular Risk in Diabetes [ACCORD] for statin plus fibrate; Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes [AIM HIGH] for statin plus extended-release niacin). Until the results of these clinical trials become available, for high-risk individuals who have a persistent elevation of TC/HDL-C despite achieving the primary LDL-C target of ≤ 2.0 mmol/L, niacin or fibrates can be added to statin therapy at the physician's discretion.

ADDITIONAL LIPID MARKERS OF CVD RISK

Apo B, Apo B/Apo A1 ratio

There is 1 apolipoprotein B molecule (apo B) per LDL, very low-density lipoprotein and intermediate-density lipoprotein particle (all of which are atherogenic). Apo B has repeatedly been shown to be a better risk marker for CVD events than LDL-C; consequently, the measurement of apo B and its monitoring in response to lipid-lowering therapy has been advocated by some (48). The measurement of apo B is most clinically useful in the individual with hyper-TG, since it provides an indication of the total number of atherogenic lipoprotein particles in the circulation. In such cases, knowledge of the apo B level may guide the aggressiveness with which lipid-lowering therapy is pursued (i.e. more aggressive therapy in individuals in whom the apo B level is elevated). An optimal level of apo B in high-risk individuals has not yet been precisely determined, but based on available evidence can be considered to be $\sim < 0.9$ g/L (49).

Apo A1 is a surrogate marker of the number of HDL particles in the circulation (there may be 2 to 4 apo A1 molecules per HDL particle). The apo B/apo A1 ratio was recently found to be the best predictor of CVD risk, accounting for 50% of population-attributable events in a population without diabetes (although its comparison to the TC/HDL-C ratio as a risk predictor was not reported in that study) (50).

There are, however, some limitations to the use of these measures in guiding clinical decision-making. While both apo B and the apo B/apo A1 ratio have been shown to predict CVD events, there is no clinical trial evidence for specific targets for these indices in individuals with or without diabetes. In addition, although standardized, the measurement of apo B and apo A1 is currently not widely available in Canada.

RECOMMENDATIONS

1. People with type 1 or type 2 diabetes should be encouraged to adopt a healthy lifestyle to lower their risk of CVD. This entails adopting healthy eating habits, achieving and maintaining a healthy weight, engaging in regular physical activity and smoking cessation [Grade D, Consensus].
2. Fasting lipid levels (TC, HDL-C, TG and calculated LDL-C) should be measured at the time of diagnosis of diabetes and then every 1 to 3 years as clinically indicated. More frequent testing should be performed if treatment for dyslipidemia is initiated [Grade D, Consensus].
3. Individuals at high risk of a vascular event should be treated with a statin to achieve an LDL-C ≤ 2.0 mmol/L [Grade A, Level 1 (20,22), Level 2 (24)]. Clinical judgement should be used as to whether additional LDL-C lowering is required for those with an on-treatment LDL-C of 2.0 to 2.5 mmol/L [Grade D, Consensus].
4. The primary target of therapy is LDL-C [Grade A, Level 1 (20,22), Level 2 (24)]; the secondary target is TC/HDL-C ratio [Grade D, Consensus].
5. If the TC/HDL-C ratio is ≥ 4.0 , consider strategies to achieve a TC/HDL-C ratio < 4.0 [Grade D, Consensus], such as improved glycemic control, intensification of lifestyle modifications (weight loss, physical activity, smoking cessation) and, if necessary, pharmacologic interventions [Grade D, Consensus].
6. If serum TG is > 10.0 mmol/L despite best efforts at optimal glycemic control and other lifestyle interventions (e.g. weight loss, restriction of refined carbohydrates and alcohol), a fibrate should be prescribed to reduce the risk of pancreatitis [Grade D, Consensus]. For those with moderate hyper-TG (4.5 to 10.0 mmol/L), either a statin or a fibrate can be attempted as first-line therapy, with the addition of a second lipid-lowering agent of a different class if target lipid levels are not achieved after 4 to 6 months on monotherapy [Grade D, Consensus].
7. For individuals not at target(s) despite optimally dosed first-line therapy as described above, combination therapy can be considered. Although there are as yet no completed trials demonstrating clinical outcomes in subjects receiving combination therapy, pharmacologic treatment options include (listed in alphabetical order):
 - Statin plus ezetimibe [Grade B, Level 2 (51)].
 - Statin plus fibrate [Grade B, Level 2 (46), Level 3 (45)].
 - Statin plus niacin [Grade B, Level 2 (33)].
8. Plasma apo B can be measured, at the physician's discretion, in addition to LDL-C and TC/HDL-C ratio, to monitor adequacy of lipid-lowering therapy in the high-risk individual [Grade D, Consensus]. Target apo B should be < 0.9 g/L [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

- Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories, p. S10
- Physical Activity and Diabetes, p. S37
- Nutrition Therapy, p. S40
- Management of Obesity in Diabetes, p. S77
- Identification of Individuals at High Risk of Coronary Events, p. S95
- Screening for the Presence of Coronary Artery Disease, p. S99
- Vascular Protection in People With Diabetes, p. S102
- Treatment of Hypertension, p. S115
- Management of Acute Coronary Syndromes, p. S119
- Treatment of Diabetes in People With Heart Failure, p. S123
- Type 1 Diabetes in Children and Adolescents, p. S150
- Type 2 Diabetes in Children and Adolescents, p. S162

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Treatment of Hypertension

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- In the prevention of diabetes-related complications, vascular protection (using a multifaceted, comprehensive approach to risk reduction) is the first priority, followed by control of hypertension in those whose blood pressure (BP) levels remain above target, then nephroprotection for those with proteinuria despite the above measures.
- People with diabetes and elevated BP should be aggressively treated to achieve a target BP of <130/80 mm Hg to reduce the risk of both micro- and macrovascular complications.
- Most people with diabetes will require multiple BP-lowering medications to achieve BP targets.

INTRODUCTION

Most people with diabetes will develop hypertension (1), which is a major determinant of both microvascular and cardiovascular (CV) complications. In the United Kingdom Prospective Diabetes Study (UKPDS), the risk of microvascular disease rose 13% for each 10 mm Hg rise in systolic blood pressure (BP) (2). CV risk is 2 to 7 times higher in people with diabetes (3-5), and up to 75% of this risk may be attributable to the presence of hypertension (6,7). In the UKPDS, the risk of both myocardial infarction (MI) and death rose by 12% for every 10 mm Hg increase in systolic BP (2).

Hypertension is a treatable risk factor. Recent studies suggest that a delay in the recognition and management of hypertension, particularly in high-risk individuals, increases their risk of CV morbidity and mortality (8-10). Therefore, people with diabetes should be regularly screened (i.e. at every diabetes-related clinic visit) for the presence of hypertension, and those with elevated BP should be aggressively treated to achieve target BP values in order to reduce the risk of both the micro- and macrovascular complications of diabetes.

In the prevention of diabetes-related complications, vascular protection (using a multifaceted, comprehensive approach to risk reduction) is the first priority, followed by control of hypertension in those whose BP levels remain above target, then nephroprotection for those with proteinuria despite the above measures (See "Vascular Protection in People With Diabetes," p. S102).

BP TARGETS

The recommended BP targets are <130/80 mm Hg and apply regardless of whether nephropathy is present or not. The Hypertension Optimal Treatment (HOT) Trial (11) and UKPDS (12) provide level 2 evidence for a diastolic BP target of <80 mm Hg. In both trials, subjects with diabetes were randomized to treatments that yielded different mean diastolic BP values (HOT: 85, 83 and 81 mm Hg; UKPDS: 87 and 82 mm Hg). Clinically important reductions in micro- and macrovascular complications (11,12), CV death (11) and diabetes-related death (12) were seen in the lowest BP groups.

The evidence for a systolic target of 130 mm Hg is weaker and includes 2 prospective cohort studies (2,13) and the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) randomized controlled trial (RCT) (14). In these studies, direct relationships were seen between higher systolic BP levels and death, coronary artery disease (CAD), nephropathy and proliferative retinopathy (2,13). The Pittsburgh Epidemiology of Diabetes Complications Study (13), a prospective cohort study of subjects with type 1 diabetes, reported statistically significant associations between CV complications and mortality as systolic BP rose above 115 mm Hg and as diastolic BP rose above 80 mm Hg. Although this relationship extended to systolic BP values <130 mm Hg, the current evidence lacked the strength to identify and recommend a systolic target lower than 130 mm Hg.

Results from the normotensive ABCD trial, in which persons with diabetes were randomized to either a moderate treatment strategy (achieved mean BP of 137/81 mm Hg) or an intensive treatment strategy (achieved mean BP of 128/75 mm Hg) also support a systolic target of 130 mm Hg (14). Although no difference was seen between the 2 groups in the prespecified primary outcome (creatinine clearance), statistically significant reductions in risks for other complications, including selected measures of nephropathy, retinopathy and stroke, occurred in the intensively treated subjects. However, because a large number of secondary endpoints were tested for significance without adjustment for multiple comparisons, and because estimates of treatment effects for some secondary outcomes were based on small numbers (e.g. strokes) and were therefore unstable, the ABCD Trial findings have not been accorded level 1 status. Stronger evidence for an optimal systolic BP awaits completion of the Action to Control Cardiovascular Risk in Diabetes

RECOMMENDATIONS

1. Blood pressure should be measured at every diabetes clinic visit for the assessment of hypertension [Grade D, Consensus].
2. Hypertension should be diagnosed in people with diabetes according to national hypertension guidelines (<http://www.hypertension.ca/chep>) [Grade D, Consensus].
3. Persons with diabetes and hypertension should be treated to attain systolic BP <130 mm Hg [Grade C, Level 3 (2,13,14)] and diastolic BP <80 mm Hg [Grade B, Level 2 (11,12)]. These target BP levels are the same as the BP treatment thresholds [Grade D, Consensus].
4. Lifestyle interventions to reduce BP should be considered, including achieving and maintaining a healthy weight and limiting sodium and alcohol intake [Grade D, Consensus]. Lifestyle recommendations should be initiated concurrently with pharmacological intervention to reduce BP [Grade D, Consensus].
5. For persons with diabetes and normal urinary albumin excretion and without chronic kidney disease, with BP \geq 130/80 mm Hg, despite lifestyle interventions:
 - Any of the following medications (listed in alphabetical order) is recommended, with special consideration to ACE inhibitors and ARBs given their additional renal benefits [Grade D, Consensus, for the special consideration to ACE inhibitors and ARBs]:
 - ACE inhibitor [Grade A, Level 1A (19)]
 - ARB [Grade A, Level 1A (20); Grade B, Level 2, for non-left ventricular hypertrophy (20)]
 - DHP CCB [Grade B, Level 2 (22)]
 - Thiazide-like diuretic [Grade A, Level 1A (22)]
 - If the above drugs are contraindicated or cannot be tolerated, a cardioselective beta blocker [Grade B, Level 2 (21)] or non-DHP CCB [Grade B, Level 2 (23)] can be substituted.
 - Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy [Grade C, Level 3 (12,22)].
 - Add-on drugs should be chosen from the first-line choices listed above [Grade D, Consensus].
6. For people with diabetes and albuminuria (persistent albumin to creatinine ratio [ACR] \geq 2.0 mg/mmol in men and \geq 2.8 mg/mmol in women), an ACE inhibitor or an ARB is recommended as initial therapy [Grade A, Level 1A (15-18)]. If BP remains \geq 130/80 mm Hg despite lifestyle interventions and the use of an ACE inhibitor or ARB, additional antihypertensive drugs should be used to obtain target BP [Grade D, Consensus].
7. For persons with diabetes and a normal urinary albumin excretion rate, with no chronic kidney disease and with isolated systolic hypertension, a long-acting DHP CCB [Grade C, Level 3 (26)] is an alternative initial choice to an ACE inhibitor [Grade B, Level 2 (19)], an ARB [Grade B, Level 2 (20)] or a thiazide-like diuretic [Grade B, Level 2 (22,25)].
8. Alpha-blockers are not recommended as first-line agents for the treatment of hypertension in persons with diabetes [Grade A, Level 1A (27)].

(ACCORD) trial, in which thousands of people with diabetes are being randomized to systolic BP targets of <120 or <140 mm Hg.

Note that the recommended BP targets are based on office determinations. Although the concept of home BP monitoring and 24-hour continuous ambulatory BP monitoring to guide treatment in people with diabetes is attractive, the role of such techniques remains unclear.

TREATMENT OF HYPERTENSION

Concurrent with lifestyle modification, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) is recommended as initial therapy. This is based, in part, on several randomized trials that have established the capacity of both drug classes to prevent major renal outcomes in subjects with diabetic nephropathy (15-18). The recommendations are also founded on the diabetic substudy of the Heart Outcomes Prevention Evaluation (MICRO-HOPE) (ramipril vs. placebo) (19) and the Losartan Intervention for Endpoint Reduction (LIFE) study (losartan vs. atenolol) (20). In these trials, people with diabetes were clearly identified as a subgroup of a priori interest, and large reductions in major prespecified outcomes, including all-cause mortality (19,20), CV mortality (19,20) and nonfatal CV events (19,20), were seen in subjects given an ACE inhibitor or an ARB. The use of atenolol as an active comparator in LIFE does not weaken conclusions about the benefits of ARBs, because atenolol had previously been shown to reduce major CV outcomes in individuals with diabetes and hypertension (12,21).

Recommendations for the use of dihydropyridine (DHP) calcium channel blockers (CCBs) and thiazide-like diuretics are based on the results of the clinical outcomes in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) substudy (22) in people with diabetes. This study in 13 101 subjects with hypertension and diabetes was prespecified in the protocol and showed no significant differences in the incidence of the primary outcome (fatal coronary heart disease and nonfatal MI) for those assigned to a thiazide-like diuretic compared to an ACE inhibitor or a DHP CCB as first-line therapy.

The antihypertensive drugs recommended as second-line therapy are supported by several generally less definitive studies. For example, the apparent equivalence of captopril and atenolol in the UKPDS (which was insufficiently powered to detect a difference) warrants a grade B recommendation for cardioselective beta blockers (21). The International Verapamil-Trandolapril Study (INVEST), an RCT of 22 576 patients with CAD and hypertension, compared atenolol- to verapamil-based treatment with the addition of an ACE inhibitor in 80 and 75% of cases, respectively. A prespecified analysis of subjects with diabetes found no differences in the first occurrence of the primary outcomes of death and fatal and nonfatal strokes (23).

Add-on therapy consists of combinations of first-line therapies. The results of a large RCT, the Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation (ADVANCE) trial, which assessed the fixed combination of an ACE inhibitor (perindopril) plus a thiazide-like diuretic (indapamide) vs. placebo in 11 140 individuals with type 2 diabetes, were recently published (24). Mean entry BP was $145 \pm 22 / 81 \pm 11$ mm Hg, and 75% of the patients were receiving BP-lowering medication prior to the addition of the combination or placebo. A mean systolic BP reduction of 5.6 mm Hg (95% CI, 5.2–6.0) and a mean diastolic BP reduction of 2.2 mm Hg (95% CI, 2.0–2.4) were associated with a reduction in total and CV mortality. No other trials have specifically compared various second-line medications in hypertensive patients with diabetes.

The key objective in the management of hypertension is to obtain systolic and diastolic BP targets, and multiple drugs will often be needed to meet such targets. Specifically, direct relationships have been seen between the size of the incremental BP reduction and the subsequent reduction in hypertension-related complications (2,13,24). For example, in the UKPDS, 29% of subjects randomized to tight BP control required ≥ 3 antihypertensive drugs by the trial's end (12). In ALLHAT (22), the mean number of medications was >2 , and up to one-third of subjects required >3 medications. Thus, any BP reduction was associated with a lower risk of complications, but larger BP reductions were associated with larger reductions in risk and required multiple medications.

Two studies have looked post hoc at the effects of thiazide-like diuretics (Systolic Hypertension in the Elderly Program [SHEP]) (25) and long-acting DHP CCBs (Systolic Hypertension in Europe [Syst-Eur] Trial) (26) in subjects with isolated systolic hypertension and diabetes. In both cases, there were statistically significant reductions in CV events.

The recommendation to avoid alpha-blockers as monotherapy or as add-on therapy ahead of other antihypertensive classes is based on ALLHAT, in which the alpha-blocker arm of the trial was stopped early because of a significantly higher risk for stroke and combined CV events compared to subjects randomized to diuretic therapy (27).

OTHER RELEVANT GUIDELINES

Physical Activity and Diabetes, p. S37

Nutrition Therapy, p. S40

Identification of Individuals at High Risk of Coronary Events, p. S95

Screening for the Presence of Coronary Artery Disease, p. S99

Vascular Protection in People With Diabetes, p. S102

Chronic Kidney Disease in Diabetes, p. S126

RELATED WEBSITES

Canadian Hypertension Education Program. Available at: <http://www.hypertension.ca/chep>. Accessed September 1, 2008.

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Management of Acute Coronary Syndromes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by David Fitchett MD FRCPC

KEY MESSAGES

- Diabetes is an independent predictor of increased short- and long-term mortality, recurrent myocardial infarction (MI) and the development of heart failure in patients with acute MI (AMI).
- Patients with an AMI and hyperglycemia should receive insulin-glucose infusion therapy to maintain blood glucose between 7.0 and 10.0 mmol/L for at least 24 hours, followed by multidose subcutaneous insulin for at least 3 months.
- People with diabetes are less likely to receive recommended treatment such as revascularization, thrombolysis, beta blockers or acetylsalicylic acid (ASA) than people without diabetes. Efforts should be directed at promoting adherence to existing proven therapies in the high-risk patient with MI and diabetes.

INTRODUCTION

Acute myocardial infarction (AMI) is responsible for about 11% of deaths in Canada each year. This represents about half of all deaths attributable to coronary artery disease (1). Approximately 30% of hospital admissions for AMI are in patients with diabetes (2-6). The hospital admission rates for AMI, corrected for age and sex differences, are over 3-fold higher in patients with diabetes (7). Diabetes is an independent predictor of increased short- and long-term mortality, recurrent MI and the development of heart failure in patients with AMI (8-10). Predictors of 1-year mortality in the person with diabetes and AMI include blood glucose (BG) level at hospital admission, age, blood pressure (BP), prior MI, duration of diabetes, insulin therapy and urine albumin level (11,12).

THERAPEUTIC STRATEGIES IN ACUTE CORONARY SYNDROMES

Guidelines for the management of patients with acute coronary syndromes (ACS) have been developed by the American College of Cardiology/American Heart Association (13-15) and the European Society of Cardiology (16). In most situations, there are no clinical trials that specifically address management of the patient with diabetes and ACS. However, subgroup analyses in patients with diabetes and ACS show either a similar or enhanced benefit from treatment compared to the overall group for a) reperfusion with fibrinoly-

sis (17) or primary angioplasty (18,19) for ST-segment elevation ACS; and b) high-risk non-ST-segment elevation ACS with an early invasive strategy (20), the use of dual antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel (21), and glycoprotein IIb/IIIa inhibitors in patients with non-ST segment elevation ACS (22).

ISSUES IN THE MANAGEMENT OF THE PATIENT WITH DIABETES AND ACS

Thrombolysis and ocular hemorrhage

There is concern that the risk of ocular hemorrhage is increased in the person with diabetes. In the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO 1) trial, there was no intra-ocular hemorrhage in the more than 6000 patients with diabetes who received thrombolytic therapy (23). Intra-ocular hemorrhage is an extremely rare complication of diabetes; consequently, diabetic retinopathy should not be considered a contraindication to fibrinolysis in patients with ST-segment elevation MI (STEMI) and diabetes (23).

Glycemic control

Hyperglycemia in the early hours after presentation is associated with increased in-hospital and 6-month mortality, independent of the presence of diabetes (24-26), and admission BG is an independent predictor of survival after AMI (25). The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) study (27-32) indicated that tight glycemic control with the use of intravenous insulin in the early hours after presentation, followed by multidose subcutaneous insulin treatment over the subsequent months, resulted in a 30% reduction in 1-year mortality. The DIGAMI 2 study (33) failed to achieve the study goals, both in the number of patients recruited and in glycemic control, but despite these limitations, it did demonstrate that outcomes were closely related to glycemic control, however achieved. Studies have shown that glucose-insulin-potassium infusion in patients with AMI do not improve outcomes. However, these protocols often resulted in increased BG levels, and therefore cannot be used as evidence for outcomes associated with glycemic control. In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study (34) of glucose and insulin in patients with AMI, patients with BG maintained <8.0 mmol/L had lower mortality than subjects with higher levels.

Long-term management

The discharge prescription for a patient with ACS includes dual antiplatelet therapy with ASA and clopidogrel, a beta-adrenergic blocker, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II antagonist (ARB) and a statin.

An ACE inhibitor should be given within the first 24 hours to patients with anterior AMI, pulmonary congestion or left ventricular ejection fraction (LVEF) <40%. Benefits from ACE inhibition are observed in patients with diabetes (35,36) who have a LVEF <40% or heart failure during hospitalization. An ARB may be used for patients who cannot tolerate an ACE inhibitor and have either clinical or radiologic signs of heart failure or LVEF <40% (37). Most patients with diabetes and ACS will benefit from ACE inhibitor or ARB therapy to prevent recurrent vascular events (see "Vascular Protection in People With Diabetes," p. S102).

Long-term beta blockade provides similar long-term benefit for the patient with or without diabetes (38,39). Mortality is reduced 23% (95% CI, 15–31%), and 42 patients treated for 2 years will result in 1 life saved (37). Beta blockers are used less often in patients with diabetes following ACS, despite a greater absolute benefit (40). Part of this care gap may result from concern that beta blockade could both prolong an episode of hypoglycemia and/or mask hypoglycemic symptoms. However, the treatment benefits outweigh this relatively small risk. Use of a beta-1 selective beta blocker (e.g. metoprolol or bisoprolol) may reduce the risk of hypoglycemia.

Treatment gap

Despite their significantly higher risk of death and recurrent vascular events, people with diabetes are less likely to be followed by a cardiologist (41) or to receive recommended evidence-based treatment such as revascularization, thrombolysis, beta blockers or ASA than people without diabetes (42-47). The treatment gap may be 1 reason for the poorer outcomes seen in the patient with diabetes. Efforts should be directed at promoting adherence to existing proven therapies in the high-risk patient with MI and diabetes. Strategies such as quality assurance assessment and structured order sheets should be developed to promote improved application of evidence-based proven therapy in the patient with MI.

OTHER RELEVANT GUIDELINES

Insulin Therapy in Type 1 Diabetes, p. S46

Pharmacologic Management of Type 2 Diabetes, p. S53

In-hospital Management of Diabetes, p. S71

Screening for the Presence of Coronary Artery Disease, p. S99

Vascular Protection in People With Diabetes, p. S102

RECOMMENDATIONS

1. In patients with diabetes and acute STEMI, the presence of retinopathy should not be a contraindication to fibrinolysis [Grade B, Level 2 (23)].
2. All patients with AMI, regardless of whether or not they have a prior diagnosis of diabetes, should have their BG level measured on admission [Grade D, Consensus]. Those with BG >12.0 mmol/L should receive insulin-glucose infusion therapy to maintain BG between 7.0 and 10.0 mmol/L for at least 24 hours, followed by multidose subcutaneous insulin for at least 3 months [Grade A, Level 1A (29,32)]. An appropriate protocol should be developed and staff trained to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia [Grade D, Consensus].
3. As beta blockers provide similar or enhanced survival benefit in patients with diabetes and MI compared to patients without diabetes, they should be prescribed and not withheld because of concern about the risks associated with hypoglycemia [Grade D, Consensus].

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Treatment of Diabetes in People With Heart Failure

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Heart failure is still underrecognized and misdiagnosed. This has significant clinical implications, as the prognosis of untreated or undertreated heart failure is poor, yet very effective proven therapies are widely available to most physicians.
- Diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy. The incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without.
- Generally, heart failure in people with diabetes should be treated similarly to heart failure in those without diabetes, although comorbidities such as renal dysfunction may be more prevalent in people with diabetes and may influence heart failure drug doses and monitoring of therapy.

INTRODUCTION

Type 2 diabetes often occurs in association with other cardiovascular risk factors such as hypertension, dyslipidemia, smoking and obesity, which together are strongly associated with atherosclerosis, ischemic heart disease and left ventricular (LV) dysfunction. LV dysfunction can be clinically silent or associated with the typical clinical signs and symptoms of heart failure (e.g. peripheral edema, shortness of breath and fatigue), although the elderly may have atypical symptoms (1). These symptoms need to be differentiated from other conditions that may have similar presentations, such as chronic obstructive pulmonary disease, pneumonia, anemia, varicose veins, depression etc.

HEART FAILURE IN PEOPLE WITH DIABETES

The diagnosis of heart failure is made by association of typical clinical signs and symptoms with objective evidence such as that obtained from a chest X-ray, an echocardiogram or plasma natriuretic peptide testing (brain natriuretic peptide [BNP] and prohormone of BNP [NT-pro-BNP]) (1). Documentation of systolic and diastolic myocardial function is recommended at the time of diagnosis of heart failure or with a significant change in clinical stability. Heart failure can occur over the entire range of LV ejection fractions (LVEFs), from <10% to >60%. The measurement of plasma BNP and NT-pro-BNP, which are acutely released by ventricular myocytes when the myocardium is stretched due to increased

filling pressures, may help make an accurate diagnosis where clinical uncertainty exists (2). However, the practising physician may still underrecognize and misdiagnose heart failure. This has significant clinical implications, as the prognosis of untreated or undertreated heart failure is poor, yet very effective proven therapies are widely available to most physicians.

Diabetes is associated with increased prevalence of heart failure, both systolic (commonly defined as an LVEF <40%) and diastolic (commonly defined as an LVEF >50%, but also referred to as preserved systolic function or preserved ejection fraction). However, the overlap between systolic and diastolic heart failure is considerable, and many people have a combination of systolic and diastolic dysfunction, although one is often reported to be predominant. Current tests such as echocardiography do usually fully characterize all aspects of systolic and diastolic dysfunction in individuals.

It is recognized that diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy (3). Epidemiological studies have shown that the incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without diabetes (4,5). While an increase in glycated hemoglobin among individuals with diabetes is a recognized risk factor for heart failure (6-10), no study to date has demonstrated that improved glycemic control significantly reduces the incidence of heart failure (11). Microalbuminuria is also an independent risk factor for heart failure, especially in people with diabetes. In individuals with and without diabetes, increasing urinary albumin to creatinine ratio is associated with a stepwise increase (2- to 4-fold) in the risk of heart failure development (8,12). Angiotensin-converting enzyme (ACE) inhibitors significantly reduce urinary albumin excretion, and in large clinical trials of subjects with cardiovascular disease or diabetes they have been shown to lower the risk of new-onset heart failure (13-15).

TREATMENT OF INDIVIDUALS WITH BOTH DIABETES AND HEART FAILURE

In most heart failure clinical trials, diabetes is present in over one-third of subjects. In the large landmark clinical trials of heart failure, there is no evidence to suggest that treatment choices for heart failure should be different in subjects with diabetes compared to those without diabetes. No large, prospective trials of heart failure have tested different heart failure drugs or doses in subjects with diabetes vs. those with-

out diabetes. Generally, heart failure in people with diabetes should be treated similarly to those without diabetes, although comorbidities such as renal dysfunction may be more prevalent in people with diabetes and may influence heart failure drug doses and monitoring of therapy. Treatment choices for diabetes (i.e. dietary and/or pharmacologic therapy) each have advantages and disadvantages in heart failure patients.

Metformin

Metformin is an effective oral antihyperglycemic agent but, based on isolated case reports and a biochemical rationale for a risk of lactic acidosis (16-18), it is approved for use under a warning in the setting of several conditions, including heart failure. Two large meta-analyses and a smaller case series have evaluated the occurrence and outcomes of lactic acidosis with the use of metformin or other antihyperglycemic agents in over 40 000 subjects, including those with heart failure. Only subjects with a serum creatinine of up to 150 $\mu\text{mol/L}$ were included in the meta-analyses, and up to 200 $\mu\text{mol/L}$ in the case series. Lactic acidosis was not increased, and cardiovascular outcomes in heart failure patients taking metformin were better than in those taking other antihyperglycemic agents. The current evidence suggests that patients with heart failure fare at least as well, if not better, with metformin than with other antihyperglycemic agents if they have only mild to moderate renal dysfunction (estimated glomerular filtration rate [eGFR] >30 mL/min). As such, metformin should still be considered as first-line therapy in heart failure patients with mild to moderate renal dysfunction (16-18).

Thiazolidinediones

Thiazolidinediones (TZDs) are known to cause fluid retention, although this is generally mild. Recent studies suggest that this is not a direct toxic effect on the myocardium. The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) study of pioglitazone in individuals at risk of cardiac ischemic events showed that TZDs were associated with fewer cardiac ischemic events, but at the cost of an increase in heart failure hospitalizations (2% absolute excess over 2.8 years, or $<1\%$ per year) (19). The recently completed Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study tested whether development of diabetes could be prevented by rosiglitazone and/or ramipril (2x2 factorial design). In >5000 subjects, a significant reduction of new glucose intolerance and cardiovascular events (0.8% absolute reduction) were seen with rosiglitazone, but a small excess of new-onset heart failure was also observed (0.4% absolute excess) (20). A recently completed randomized trial comparing the efficacy of rosiglitazone, metformin or glyburide monotherapy in people with type 2 diabetes reported a greater treatment failure rate of monotherapy with glyburide or metformin compared to rosiglitazone, but an increase in reported heart failure with rosiglitazone. When only adjudicated events were considered, there was no signifi-

cant difference in cardiovascular-related or heart failure-related mortality in any arm (21). Recent reports suggest that the fluid retention can be safely managed with careful observation, taking care not to increase diuretic therapy in the absence of either symptoms or signs of central volume overload rather than just peripheral edema (17,18). In addition to product monographs in November 2007, Health Canada advised that, "Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure, (i.e. NYHA Class I, II, III or IV)." (22) A recent meta-analysis (23) has not confirmed any difference in the risk of congestive heart failure between rosiglitazone and pioglitazone. Glitazones may be used cautiously in patients with stable mild heart failure if close specialist monitoring is available, but should not be used in patients with unstable or severe heart failure.

A detailed discussion of the rationale and evidence for the treatment approach to heart failure patients is available in the Canadian Cardiovascular Society consensus recommendations (<http://www.hfcc.ca>) (1,24).

RECOMMENDATIONS

1. Individuals with diabetes and heart failure should receive the same heart failure therapies as those identified in the evidence-based Canadian Cardiovascular Society heart failure recommendations (<http://www.hfcc.ca>) [Grade D, Consensus].
2. Unless contraindicated, metformin may be used in people with type 2 diabetes and heart failure [Grade C, Level 3 (16,17)]. Metformin should be temporarily withheld if renal function acutely worsens, and should be discontinued if renal function significantly and chronically worsens [Grade D, Consensus].
3. Physicians should be aware that people taking TZDs are at increased risk of heart failure and may present with symptoms such as increased dyspnea and peripheral edema [Grade B, Level 2 (19,20)].
4. In people with diabetes and heart failure and an eGFR <60 mL/min:
 - Starting doses of ACE inhibitors or angiotensin receptor II antagonists (ARBs) should be halved [Grade D, Consensus].
 - Serum electrolytes and creatinine, blood pressure and body weight, as well as heart failure symptoms and signs, should be monitored more frequently [Grade D, Consensus].
 - Dose up-titration should be more gradual (with monitoring of blood pressure, serum potassium and creatinine) [Grade D, Consensus].
 - The target drug doses should be those identified in the evidence-based Canadian Cardiovascular Society recommendations on heart failure (<http://www.hfcc.ca>), if well tolerated [Grade D, Consensus].
5. Beta blockers should be prescribed when indicated for systolic heart failure, as they provide similar benefits in people with diabetes compared with people without diabetes [Grade B, Level 2 (25,26)]. Where hypoglycemia is a particular concern, a selective beta blocker such as bisoprolol or metoprolol may be preferred [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Physical Activity and Diabetes, p. S37

Nutrition Therapy, p. S40

Pharmacologic Management of Type 2 Diabetes, p. S53

Screening for the Presence of Coronary Artery Disease, p. S99

Vascular Protection in People With Diabetes, p. S102

Management of Acute Coronary Syndromes, p. S119

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Chronic Kidney Disease in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Identification of chronic kidney disease (CKD) in diabetes requires screening for proteinuria, as well as an assessment of renal function.
- All individuals with CKD should be considered at high risk for cardiovascular events, and should be treated to reduce these risks.
- The progression of renal damage in diabetes can be slowed through intensive glycemic control and optimization of blood pressure. Progression of diabetic nephropathy can be slowed through the use of medications that disrupt the renin-angiotensin-aldosterone system.

INTRODUCTION

Chronic kidney disease (CKD) is one of the most common and potentially devastating complications of diabetes. Fifty percent of people with diabetes have CKD, and CKD associated with diabetes is the leading cause of kidney failure in Canada (1-4). CKD in diabetes can be due to classic diabetic nephropathy or other forms of kidney damage. Classic diabetic nephropathy progresses from subclinical disease to the earliest clinically detectable stage characterized by persistent proteinuria (2,5,6) (Figure 1). The degree of proteinuria is characterized as either microalbuminuria (urinary albumin 30 to 300 mg/day) or overt nephropathy (urinary albumin >300 mg/day) (Table 1). Typically it takes many years to progress through these

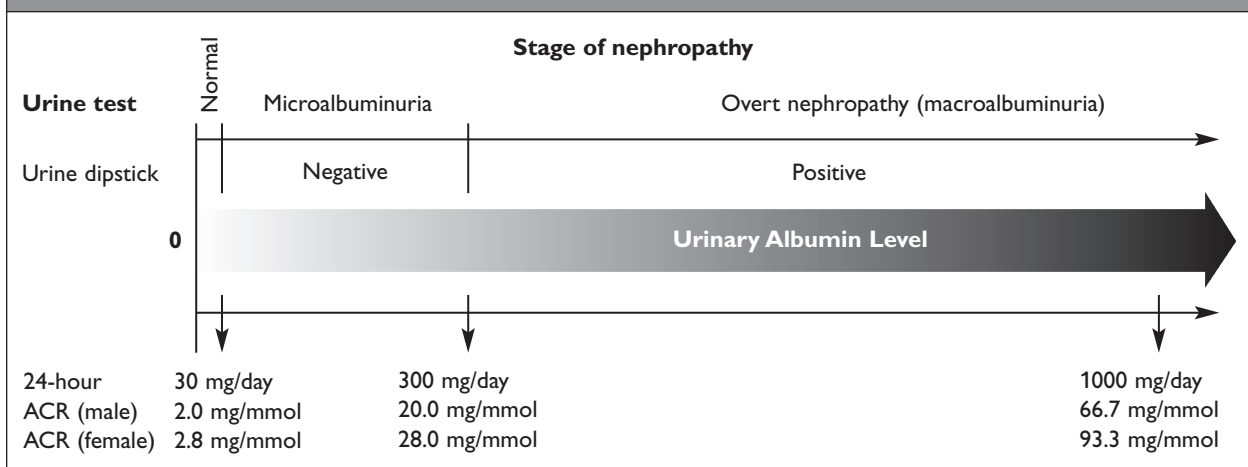
stages (2,7,8), and significant renal dysfunction is not usually seen until late in the course (9). Because type 2 diabetes can be unrecognized for a long time prior to diagnosis, it is possible for renal disease, including advanced nephropathy, to be present at the time of diagnosis of type 2 diabetes (10,11).

Although diabetic nephropathy is common, as many as 50% of people with diabetes and significant renal dysfunction have normal urinary albumin levels with renal disease that is not related to classic diabetic nephropathy (12). For example, hypertensive nephrosclerosis and renovascular disease are common causes of CKD in people with diabetes. Table 2 lists indicators that favour the presence of renovascular disease. The risk of end-stage renal disease in diabetes does not appear to vary significantly whether the kidney disease is related to diabetic nephropathy or alternative renal diagnoses (13). Thus, identification of CKD in diabetes requires screening for proteinuria, as well as an assessment of renal function.

Regardless of the cause, the stage of kidney disease can be classified based on the level of renal function (Table 3). In the case of diabetes, the kidney damage associated with stage 1 or 2 CKD manifests as persistent albuminuria (see Screening, p. S127).

It is also important to recognize that people with CKD are among those at highest risk for cardiovascular (CV) morbidity and mortality, and that interventions to lower CV risk remain the most important priority in this population (14,15).

Figure 1. Stage of diabetic nephropathy by level of urinary albumin by various test methods



ACR = albumin to creatinine ratio

Stage of nephropathy	Urine dipstick for protein	Urine ACR (mg/mmol)	24- urine collection for albumin* (mg/day)
Normal	Negative	<2.0 (men) <2.8 (women)	<30
Micro-albuminuria	Negative	2.0–20.0 (men) 2.8–28.0 (women)	30–300
Overt nephropathy (macroalbuminuria)	Positive	>20.0 (men) >28.0 (women) >66.7 (men) >93.3 (women)	>300 >1000

*Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels. ACR results may be elevated with conditions other than diabetic nephropathy (see text and Table 4)

ACR = albumin to creatinine ratio

<ul style="list-style-type: none"> • Severe or refractory hypertension • Low eGFR with normal or near-normal ACR • Low or low-normal serum potassium (especially if patient is on an ACE inhibitor or an ARB) • Flank or abdominal bruits • >30% rise in serum creatinine following initiation of an ACE inhibitor or an ARB • Presence of aortic or peripheral arterial disease • "Flash" pulmonary edema • Asymmetric renal size on ultrasound • Advanced hypertensive retinopathy
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ACE = angiotensin-converting enzyme
 ACR = albumin to creatinine ratio
 ARB = angiotensin II receptor antagonist
 eGFR = estimated glomerular filtration rate

SCREENING

Identification of CKD in diabetes is usually a clinical diagnosis, requiring a kidney biopsy only when clinical indicators leave doubt as to the diagnosis. A person with diabetes is considered to have CKD if he or she has classic diabetic nephropathy (as evidenced by persistent albuminuria regardless of level of kidney function), or significantly reduced kidney function (as evidenced by an estimated glomerular filtration rate [eGFR] ≤ 60 mL/min). Table 4 lists indicators that favour the diagnosis of either diabetic or nondiabetic nephropathy (16–19). As kidney damage is often asymptomatic until severe, screening must be performed to

Stage	Qualitative description	eGFR (mL/min)
1	Kidney damage, normal GFR	≥ 90
2	Kidney damage, mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease	<15 (or dialysis)

CKD = chronic kidney disease
 eGFR = estimated glomerular filtration rate
 GFR = glomerular filtration rate

Favours diabetic nephropathy	Favours alternate renal diagnosis
<ul style="list-style-type: none"> • Persistent albuminuria • Bland urine sediment • Slow progression of disease • Low eGFR associated with overt proteinuria • Presence of other complications of diabetes • Known duration of diabetes >5 years 	<ul style="list-style-type: none"> • Extreme proteinuria (>6 g/day) • Persistent hematuria (microscopic or macroscopic) or active urinary sediment • Rapidly falling eGFR • Low eGFR with little or no proteinuria • Other complications of diabetes not present or relatively not as severe • Known duration of diabetes ≤ 5 years • Family history of nondiabetic renal disease (e.g. polycystic kidney disease) • Signs or symptoms of systemic disease

eGFR = estimated glomerular filtration rate

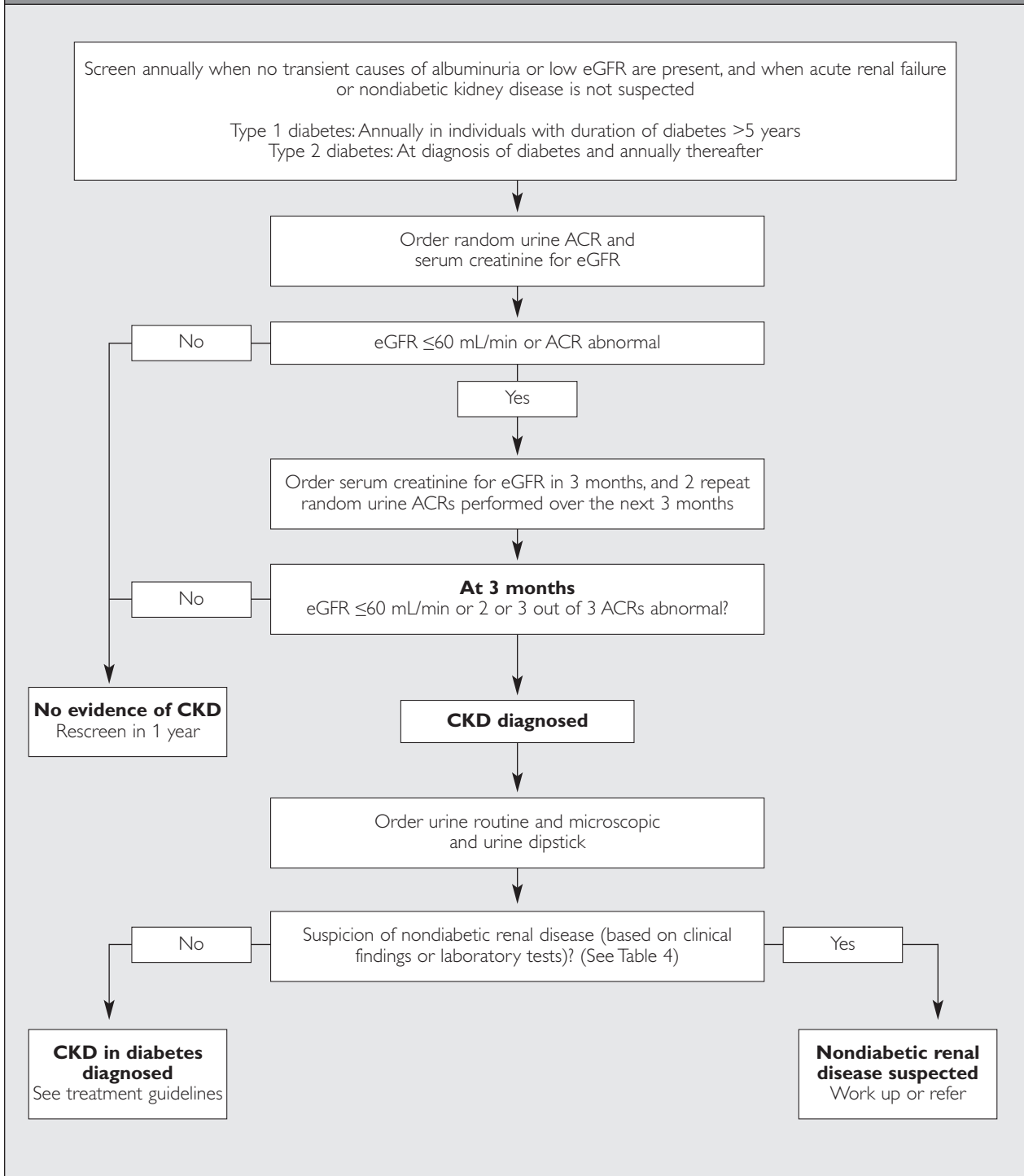
identify renal damage in order to delay or prevent loss of renal function through early initiation of effective therapies, and to manage complications in those identified with renal disease. In adults, screening is performed by measuring urinary albumin levels and estimating the level of kidney function (Figure 2).

Urine testing

Screening for microalbuminuria should be performed using a random urine test for albumin to creatinine ratio (ACR). As transient microalbuminuria unrelated to diabetic nephropathy can occur, persistent microalbuminuria (at least 2 of 3 ACR tests positive taken at 1- to 8-week intervals) should be demonstrated before the diagnosis of

nephropathy is made. Overt nephropathy rarely normalizes without treatment, and repeat ACR testing is not required to make the diagnosis of nephropathy in those with ACR values in the overt nephropathy range. A urine dipstick test should also be performed, either in the laboratory or at the point of care, as a screen for renal disease other than diabetic nephropathy.

Figure 2. Screening for CKD in adults



ACR = albumin to creatinine ratio

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

Twenty-four-hour urine collections are frequently performed incorrectly, are unpopular with patients and are unnecessary in routine diabetes care (20-24). However, a 24-hour collection can be useful when there is doubt about the accuracy of an eGFR, when screening for nonalbumin urinary proteins (e.g. multiple myeloma) or when estimating daily sodium intake in an individual with refractory edema or hypertension. Individuals should be counselled to discard the first morning urine on the day of collection, and then collect all subsequent urine for a 24-hour period, including the first morning urine of the next day.

Renal function testing

Diabetic nephropathy and damage from other conditions such as hypertension and renovascular disease can lead to a loss of renal function in people with diabetes. An estimate of the kidney's ability to filter toxins from the blood should be made. Serum creatinine is the most commonly used measure of renal function; however, the creatinine may falsely indicate that a person's renal function is normal (25,26). Individuals can lose up to 50% of their renal function before serum creatinine levels rise into the abnormal range (27). The eGFR is a more sensitive method of identifying low kidney function in people with diabetes. In Canada, the eGFR is most often calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation, which takes into account the person's serum creatinine, age and sex. Clinicians can further adjust the eGFR for race. Calculation of the MDRD glomerular filtration rate (GFR) is complicated and typically an electronic aid (either a spreadsheet or an Internet-based tool) is used, or the GFR is calculated and reported by the laboratory automatically when a serum creatinine is ordered (28).

Delaying screening for CKD

As the ACR can be elevated with recent major exercise (29), fever (30), urinary tract infection, congestive heart failure (31), menstruation or acute severe elevations of blood pressure (BP) or blood glucose (BG) (32,33), screening for albuminuria should be delayed in the presence of these conditions. Intravascular volume contraction or any acute illness can transiently lower kidney function, and GFR estimation for screening purposes should be delayed until such conditions resolve.

TREATMENT AND FOLLOW-UP

All people with CKD should be considered to be at high risk for CV events and should be treated to reduce these risks. The progression of renal damage in diabetes can be slowed through intensive glycemic control (34) and optimization of BP (35). Progression of diabetic nephropathy can be slowed through the use of medications that disrupt the renin-angiotensin-aldosterone system (RAAS) (36). BP and glycemic targets are the same as for those individuals with diabetes without nephropathy.

In addition to BP control, some antihypertensive have been shown to have additional renal-protective properties. In type 1 diabetes, angiotensin-converting enzyme (ACE) inhibitors have been shown to decrease albuminuria and prevent worsening of nephropathy (37), and angiotensin II receptor antagonists (ARBs) have been shown to reduce proteinuria (38). In type 2 diabetes, ACE inhibitors and ARBs have been shown to decrease albuminuria and prevent worsening of nephropathy, and ARBs have been shown to delay the time to dialysis in those with renal dysfunction at baseline (39-42). In type 2 diabetes, ACE inhibitors have been shown to reduce the chance of developing new nephropathy (39,43). ACE inhibitor plus ARB combination therapy has been shown to lower BP and proteinuria in type 2 diabetes more effectively than monotherapy with either agent (44-46). These renal-protective effects also appear to be present in proteinuric individuals with diabetes and normal or near-normal BP. ACE inhibitors have been shown to reduce progression of diabetic nephropathy in normotensive individuals with type 1 (47-50) or type 2 diabetes (51). In people with diabetes, hypertension and proteinuria, nondihydropyridine calcium channel blockers (non-DHP CCBs) (diltiazem and verapamil) have been shown to decrease albuminuria and are associated with a slower loss of renal function (52-55). However, non-DHP CCBs do not prevent the development of nephropathy (43).

In CKD from causes other than diabetic nephropathy, ACE inhibition has been shown to reduce proteinuria, slow progression of renal disease and delay the need for dialysis (56,57). The issue of whether ARBs and ACE inhibitors are similarly effective in CKD that is not caused by diabetic nephropathy remains controversial (58). Compared to monotherapy with either agent, ACE inhibitor plus ARB combination therapy has been shown to reduce proteinuria (59,60).

In people with CKD and diabetes with or without hypertension, an ACE inhibitor or an ARB would be the preferred initial agent for prevention of renal disease progression. To date, there have been no large-scale hard-endpoint trials for second-line agents in nephropathy (see The Role of Proteinuria Reduction, p. S130).

Treating CKD in diabetes safely

Individuals starting therapy with an ACE inhibitor or an ARB should be monitored within 1 to 2 weeks of initiation or titration of treatment for significant worsening of renal function or the development of significant hyperkalemia. Periodic monitoring should continue in those whose serum creatinine or potassium level increases above normal laboratory limits until these values have stabilized. Serum creatinine typically increases up to 30% above baseline after initiation of an ACE inhibitor or ARB, and usually stabilizes after 2 to 4 weeks of treatment (61). ACE inhibitors and ARBs can be used safely in people with renovascular disease, unless the individual has only a single functioning kid-

RECOMMENDATIONS

1. The best possible glycemic control and, if necessary, intensive diabetes management should be instituted in people with type 1 or type 2 diabetes for the prevention of onset and delay in progression to CKD [Grade A, Level 1A (34,71,72)].
2. In adults, screening for CKD in diabetes should be conducted using a random ACR and a serum creatinine converted into an eGFR [Grade D, Consensus]. Screening should be performed annually in adults with type 1 diabetes of >5 years' duration. Individuals with type 2 diabetes should be screened at diagnosis of diabetes and yearly thereafter. Screening should be delayed when causes of transient albuminuria or low eGFR are present [Grade D, Consensus].
3. People with diabetes and CKD should have a random urine ACR and a serum creatinine converted into an eGFR performed at least every 6 months [Grade D, Consensus].
4. Adults with diabetes and persistent albuminuria (ACR >2.0 mg/mmol in males, >2.8 mg/mmol in females) should receive an ACE inhibitor or an ARB to delay progression of CKD, even in the absence of hypertension [Grade A, Level 1A (37,39-42,47,48,50,51,73), for ACE inhibitor use in type 1 and type 2 diabetes, and for ARB use in type 2 diabetes; Grade D, Consensus, for ARB use in type 1 diabetes].
5. People with diabetes on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels checked within 1 to 2 weeks of initiation or titration of therapy. Potassium and serum creatinine levels should be checked in people with diabetes receiving an ACE inhibitor or ARB during times of acute illness [Grade D, Consensus].
6. The use of thiazide-like diuretics should be considered in individuals with CKD and diabetes for control of sodium and water retention, hypertension or hyperkalemia [Grade D, Consensus]. Alternatively, furosemide can be substituted for or added to thiazide-like diuretics for individuals who fail monotherapy with thiazide-like diuretics or who have severe sodium and water retention or hyperkalemia [Grade D, Consensus].
7. Consideration should be given to stopping ACE inhibitor, ARB and/or diuretic therapy during times of acute illness (e.g. febrile illness, diarrhea), especially when intravascular volume contraction is present or suspected [Grade D, Consensus]. Women should avoid becoming pregnant when receiving ACE inhibitor or ARB therapy, as the use of medications that disrupt the RAAS has been associated with adverse fetal outcomes [Grade D, Consensus].
8. A referral to a nephrologist or internist with an expertise in diabetic nephropathy should be considered if there is a chronic, progressive loss of kidney function, if the eGFR is <30 mL/minute, if the ACR is persistently >60 mg/mmol, or if the individual is unable to achieve BP targets or remain on renal-protective therapies due to adverse effects, such as hyperkalemia or a >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB [Grade D, Consensus].

ney or severe bilateral disease (62,63). However, serum creatinine and potassium levels should be monitored carefully if these medications are used when renovascular disease is suspected (64).

Individuals who develop mild to moderate hyperkalemia should receive nutritional counselling regarding a potassium-restricted diet, and consideration should be given to the use of nonpotassium-sparing diuretics (such as thiazides or furosemide). If an ACE inhibitor or ARB is not tolerated due to severe hyperkalemia, or >30% increase in serum creatinine or allergic reactions, the drug should be withdrawn and other ACE inhibitors or ARBs should not be substituted.

To avoid acute renal failure, ACE inhibitors, ARBs and diuretics should be stopped during acute illnesses associated with intravascular volume contraction. There is no upper limit of the serum creatinine level for initiation of ACE inhibitor or ARB therapy, but if the creatinine clearance is <30 mL/minute, these agents should be started with care or referral for specialized nephrologic care should be considered. As the use during pregnancy of medications that disrupt the RAAS have been associated with congenital malformations (65), women with diabetes of childbearing age should avoid pregnancy if ACE inhibitors or ARBs are required. If a woman with diabetes receiving ACE inhibitor or ARB therapy wishes to become pregnant, consideration

should be given to stopping these drugs prior to conception.

Individuals started on a non-DHP CCB should be monitored clinically for development of bradycardia. As all nephroprotective drugs are also antihypertensives, individuals should be monitored for development of hypotension.

The role of proteinuria reduction

The amount of proteinuria correlates with the likelihood of progression of many kidney diseases, including diabetic nephropathy (66-69). Individuals with an antiproteinuric response to an ACE inhibitor or an ARB are less likely to progress to renal failure (66). These findings, in combination with basic science evidence (70), suggest that proteinuria may contribute to kidney damage, and many clinicians now target proteinuria for reduction independent of BP level. However, no large-scale hard-endpoint trials in which proteinuria reduction was the primary intervention have been completed, and the role of proteinuria as a causative factor in renal damage remains controversial. Which populations should be targeted for reduction of proteinuria, the thresholds and targets for antiproteinuric therapies, and the optimal antiproteinuric drug regimens remain topics of active research. While reduction of proteinuria in diabetic nephropathy may be desirable, it is not possible to generate a clinical practice guideline in this area at this time.

Referral

Most people with CKD and diabetes will not require referral to a specialist in renal disease. However, specialist care may be necessary when renal dysfunction is severe, when there are difficulties implementing renal-protective strategies or when there are problems managing the sequelae of renal disease (see Recommendation #8).

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29

Identification of Individuals at High Risk of Coronary Events, p. S95

Vascular Protection in People With Diabetes, p. S102

Treatment of Hypertension, p. S115

Type 1 Diabetes in Children and Adolescents, p. S150

Diabetes and Pregnancy, p. S168

RELATED WEBSITES

Canadian Hypertension Society. Available at <http://www.hypertension.ca/chs>. Accessed September 1, 2008.

Canadian Society of Nephrology. Available at <http://www.csnsn.ca>. Accessed September 1, 2008.

Nephron Information Center. Available at: <http://www.nephron.com>. Accessed September 1, 2008.

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Retinopathy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Screening is important for early detection of treatable disease. Screening intervals for diabetic retinopathy vary according to the individual's age and type of diabetes.
- Tight glycemic control reduces the onset and progression of sight-threatening diabetic retinopathy.
- Laser therapy reduces the risk of significant visual loss.

INTRODUCTION

Diabetic retinopathy is the most common cause of new cases of legal blindness in people of working age (1). The Eye Diseases Prevalence Research Group determined the crude prevalence rate of retinopathy in the adult diabetic population of the United States to be 40.3%; sight-threatening retinopathy occurred at a rate of 8.2% (2). Previous data showed the prevalence rate of proliferative retinopathy to be 23% in people with type 1 diabetes, 14% in people with type 2 diabetes and on insulin therapy, and 3% in people receiving oral antihyperglycemic therapies (3). Macular edema occurs in 11, 15 and 4% of these groups, respectively (4). First Nations populations in Canada have high rates of diabetes and its complications (5,6). It is estimated that approximately 2 million individuals in Canada (i.e. almost all people with diagnosed diabetes) have some form of diabetic retinopathy (7).

Visual loss is associated with significant morbidity, including increased falls, hip fractures and a 4-fold increase in mortality (8). Among individuals with type 1 diabetes, limb amputation and visual loss due to diabetic retinopathy are the 2 independent predictors of early death (9).

DEFINITION AND PATHOGENESIS

Diabetic retinopathy is clinically exclusively defined, diagnosed and treated based on the extent of retinal vascular disease. Three distinct forms of diabetic retinopathy are described: 1) macular edema, which includes diffuse or focal vascular leakage at the macula; 2) progressive accumulation of blood vessel change that includes microaneurysms, intraretinal hemorrhage, vascular tortuosity and vascular malformation (together known as nonproliferative diabetic retinopathy) that ultimately leads to abnormal vessel growth (proliferative diabetic retinopathy); and 3) retinal capillary closure, a form of vascular change detected by fluorescein angiography, which

is also well recognized as a potentially blinding complication of diabetes, but currently has no treatment options.

SCREENING AND DIAGNOSIS

Since laser therapy for sight-threatening diabetic retinopathy reduces the risk of blindness (10-13), ophthalmic screening strategies are intended to detect treatable disease. Sight-threatening diabetic retinopathy includes severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy or clinically significant macular edema. Screening programs consider the differences in incidence and prevalence of retinopathy observed in type 1 and type 2 diabetes, and distinguish between children and adults (see Table 1) (14-19).

Diabetic retinopathy rarely develops in children with type 1 diabetes <10 years of age, regardless of the duration of diabetes (18). Among patients <15 years of age, irrespective of age of onset of diabetes, the prevalence of mild nonprolif-

Table 1. Screening for retinopathy

When to initiate screening

- 5 years after diagnosis of type 1 diabetes in all individuals ≥ 15 years
- In all individuals at diagnosis of type 2 diabetes

Screening methods

- 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard)
- Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil
- Digital fundus photography

If retinopathy is present

- Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less)
- Treat sight-threatening retinopathy with laser therapy
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
- Screen for other diabetes complications

If retinopathy is not present

- Type 1 diabetes: rescreen annually
- Type 2 diabetes: rescreen every 1–2 years
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
- Screen for other diabetes complications

*See Other Relevant Guidelines, p. S136

BP = blood pressure

erative retinopathy was 2%, and none had sight-threatening diabetic retinopathy (11,18,20). However, the prevalence rate increases sharply after 5 years' duration of diabetes in post-pubertal individuals with type 1 diabetes (18). In the Wisconsin Epidemiology Study of Diabetic Retinopathy 4-year incidence study, no person <17 years of age developed proliferative retinopathy or macular edema (16,21,22). Conversely, in people with type 2 diabetes, retinopathy may be present in 21 to 39% of patients soon after clinical diagnosis, but is sight-threatening in only about 3% (4,17,19,23). In the United Kingdom Prospective Diabetes Study (UKPDS), few patients without retinopathy at diagnosis of diabetes had disease progression to the point of requiring photocoagulation in the following 3 to 6 years (24). More recently, progression rates of diabetic retinopathy were prospectively evaluated (14,15,25). The Liverpool Diabetic Eye Study reported the 1-year cumulative incidence of sight-threatening diabetic retinopathy in individuals with type 1 or type 2 diabetes who at baseline had no diabetic retinopathy, had background retinopathy, or had mild preproliferative retinopathy. In people with type 1 diabetes, the incidence in these groups was 0.3, 3.6 and 13.5%, respectively (14), and in individuals with type 2 diabetes it was 0.3, 5.0 and 15.0%, respectively (15). Although the incidence of sight-threatening diabetic retinopathy in the group without baseline diabetic retinopathy is low (14,15,24,25), there have been no studies comparing various screening intervals in their effectiveness to reduce the risk of vision loss (26).

The gold standard for diagnosing diabetic retinopathy is stereoscopic colour fundus photographs in 7 standard fields (27). However, practical common screening strategies for diabetic retinopathy include clinical examination with ophthalmoscopy with or without diagnostic tools such as fundus photography. The accuracy of direct ophthalmoscopy to assess severity of retinopathy can vary widely (28) and is deemed inadequate through an undilated pupil (29-31). Combining direct ophthalmoscopy with slit-lamp fundus biomicroscopy, diagnostic accuracy was comparable to the gold standard of 7-field stereophotography (32). Optical coherence tomography (OCT) is also currently under investigation for its use in the diagnosis of diabetic macular edema (33,34). Telemedicine programs are widely employed in Canada and internationally for the identification and triage of patients with diabetic retinopathy (35).

PREVENTION OF ONSET AND PROGRESSION

Longer duration of diabetes, elevated glycated hemoglobin (A1C), increased blood pressure (BP), dyslipidemia, low hematocrit, pregnancy (with type 1 diabetes) and severe retinopathy itself are associated with disease progression (16-19,22,36-41).

Glycemic control

In the Diabetes Control and Complications Trial, intensive

insulin therapy in people with type 1 diabetes reduced the risk of onset of retinopathy by 76%, and the rate of progression by 54%, compared to conventional therapy (42,43). In type 1 diabetes, rapid improvement of glycemic control may be associated with transient early worsening of retinopathy during the first 12 months, but this effect is offset by long-term gain (44).

The UKPDS demonstrated that in type 2 diabetes, hyperglycemia is an independent risk factor for the incidence and progression of retinopathy (45,46). Tight glycemic control is therefore recommended (45,47).

Anecdotal reports and retrospective analyses of individuals receiving thiazolidinediones (TZDs) suggest a correlation with increased diabetic macular edema (48,49). Individuals who experience changes in vision while on a TZD should be referred to an ophthalmologist for assessment.

BP control

In type 1 and type 2 diabetes, elevated diastolic BP is a significant risk factor for the development of macular edema (22,50), and elevated systolic BP is a risk factor for vision loss (51). In hypertensive individuals, development and progression of retinopathy can be reduced by treatment with antihypertensive agents (52). Further lowering of BP in normotensive people with type 2 diabetes also reduces the progression of retinopathy (53).

Lipid control

Dyslipidemia is an independent risk factor for retinal hard exudates and clinically significant macular edema in type 1 diabetes (54). Similarly, in the Early Treatment Diabetic Retinopathy Study (ETDRS) trial, in which most participants had type 2 diabetes, elevated low-density lipoprotein cholesterol was associated with increased risk of developing hard exudates (38).

TREATMENT

Treatment for diabetic retinopathy includes retinal photocoagulation and vitreoretinal surgery.

Residual vision can often be improved by an accurate spectacle correction and/or magnifying aids, with instructions for use. People with impaired vision should be informed of the services in their community that will assist with retraining for employment, encourage independence and improve their quality of life (55,56).

Laser therapy

As determined in the Diabetic Retinopathy Study (DRS) and the ETDRS, laser therapy by panretinal photocoagulation to the retinal periphery reduces severe visual loss and reduces legal blindness by 90% in people with severe nonproliferative or proliferative retinopathy (11-13). As determined by the ETDRS, focal and/or grid laser treatment to the macula for clinically significant macular edema reduces the incidence

of moderate visual loss by 50% (10). The first study to evaluate the long-term outcome of laser treatment confirmed its benefit (57).

Surgical intervention

The Diabetic Retinopathy Vitrectomy Study (DRVS) Group evaluated the benefit of early vitrectomy (<6 months) in the treatment of severe vitreous hemorrhage (58) and very severe proliferative diabetic retinopathy (59). People with type 1 diabetes of <20 years' duration and severe vitreous hemorrhage were more likely to achieve good vision with early vitrectomy compared to conventional management (58). Similarly, early vitrectomy was associated with a higher chance of visual recovery in people with either type 1 or 2 diabetes with very severe proliferative diabetic retinopathy (59). Surgical advances in vitrectomy since the DRVS trials have demonstrated reduced side effects with more consistent favourable visual outcomes, thus supporting vitrectomy in advanced proliferative diabetic retinopathy (60). Furthermore, these advances have expanded surgical indications to include vitrectomy for diffuse macular edema, resulting in structural and functional improvements (61). It is worth noting that systemic treatment with acetylsalicylic acid (ASA) does not increase the risk or severity of vitreous hemorrhage (62-64). The risk of vitreous hemorrhage or foveola blot hemorrhage associated with warfarin therapy is unknown.

Pharmacologic intervention

Studies investigating local and systemic pharmacologic treatments for diabetic retinopathy are underway, but to date no phase III clinical trial has been successful in achieving its primary endpoint. Nonetheless, earlier phase studies strongly suggested that intra-ocular delivery of anti-vascular endothelial growth factor (anti-VEGF) agents or steroid could be effective in reducing diabetic macular edema or retinal neovascularization. In particular, pegaptanib, an anti-VEGF aptamer approved for the treatment of "wet" age-related macular degeneration, has been shown, in a phase II trial (65) and a pilot study (66), to reduce diabetic macular edema and improve visual outcomes compared to control interventions. A retrospective review of patients treated for edema demonstrated a reduction in neovascularization (67). Similarly, a meta-analysis by the Cochrane Collaboration (68) supports the intravitreal injection of the steroid triamcinolone acetate (69-71), or the use of implanted intra-ocular devices that release fluocinolone acetonide (72,73) or dexamethasone (74). Finally, 3 phase III clinical trials that are evaluating the effects of renin-angiotensin-aldosterone system blockade are nearing completion, and are of particular note. These are the Diabetic Retinopathy Candesartan Trial (DIRECT) (75), the retinal measurement substudy (AdRem) of the Action in Diabetes in Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (76) and the Renin Angiotensin System Study (RASS) (77). These studies are

based upon data from the EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus (EUCLID) (78) and the United Kingdom Prospective Diabetes Study (UKPDS) (79). The EUCLID study, designed to evaluate renal disease, demonstrated that the odds ratio for risk of progression of diabetic retinopathy was 0.5 in patients treated with angiotensin-converting enzyme (ACE) inhibitors compared to those treated with placebo. However, this study was underpowered for ophthalmic outcomes. Similarly, the UKPDS suggested a reduction in the need for laser therapy in patients with type 2 diabetes who received an angiotensin II receptor blocker. Taken together, better understanding of the mechanisms of diabetic retinopathy and recent development of pharmacologic therapies for other indications suggest that new therapies are on the horizon.

RECOMMENDATIONS

1. In individuals ≥ 15 years of age with type 1 diabetes, screening and evaluation for retinopathy by an expert professional should be performed annually starting 5 years after the onset of diabetes [Grade A, Level 1 (16,18)].
2. In individuals with type 2 diabetes, screening and evaluation for diabetic retinopathy by an expert professional should be performed at the time of diagnosis of diabetes [Grade A, Level 1 (17,21)]. The interval for follow-up assessments should be tailored to the severity of the retinopathy. In those with no or minimal retinopathy, the recommended interval is 1 to 2 years [Grade A, Level 1 (17,21)].
3. Screening for diabetic retinopathy should be performed by experienced professionals, either in person or through interpretation of retinal photographs taken through dilated pupils [Grade A, Level 1 (31)].
4. To prevent the onset and delay the progression of diabetic retinopathy, people with diabetes should be treated to achieve optimal control of blood glucose [Grade A, Level 1A (42,45)] and BP [Grade A, Level 1A (52)]. People with abnormal lipids should be considered at high risk for retinopathy [Grade A, Level 1 (54)].
5. Patients with sight-threatening diabetic retinopathy should be assessed by a general ophthalmologist or retina specialist [Grade D, Consensus]. Laser therapy and/or vitrectomy [Grade A, Level 1A (10,12,58,59)] and/or pharmacologic intervention [Grade B, Level 2 (65)] should be considered.
6. Visually disabled people should be referred for low-vision evaluation and rehabilitation [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29

Dyslipidemia, p. S107

Treatment of Hypertension, p. S115

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

Diabetes and Pregnancy, p. S168

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Neuropathy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Vera Bril MD FRCPC and Bruce Perkins MD MPH FRCPC

KEY MESSAGES

- Exposure to higher levels of glycemia, elevated triglycerides, high body mass index, smoking and hypertension are risk factors for neuropathy.
- Intensive glycemic control is effective for primary prevention or secondary intervention of neuropathy in people with type 1 diabetes.
- In people with type 2 diabetes, lower blood glucose levels are associated with reduced frequency of neuropathy.

INTRODUCTION

Detectable sensorimotor polyneuropathy will develop within 10 years of the onset of diabetes in 40 to 50% of people with type 1 or type 2 diabetes (1). Although <50% of these patients have motor or sensory symptoms, the neuropathic pain associated with symptomatic disease is frequently bothersome (2,3). While neuropathy is uncommon in people with type 1 diabetes within the first 5 years after onset of diabetes, people with type 2 diabetes may have neuropathy at the time of diagnosis (4). Risk factors for neuropathy are exposure to higher levels of glycemia, elevated triglycerides, high body mass index, smoking and hypertension (5). Foot ulceration, which depends on the degree of foot insensitivity (6), and amputation are important and costly sequelae of diabetic neuropathy (7). Both somatic and autonomic neuropathy may occur, and may require referral to a specialist experienced in managing the affected body system. Mononeuropathy, particularly carpal tunnel syndrome, is common in people with diabetes and can be difficult to diagnose (8).

Underdiagnosis of neuropathy is a fundamental problem in the primary care of people with diabetes, and impedes the benefits of early identification, the management necessary to achieve improved glycemic control and the prevention of neuropathy-related sequelae (9).

SCREENING FOR PERIPHERAL NEUROPATHY

Screening for neuropathy can be performed rapidly and reliably using the 10-g Semmes-Weinstein monofilament or 128-Hz tuning fork (10-13). Methods for using the monofilament or tuning fork to detect diabetic neuropathy are

explained in Appendix 4. Other screening maneuvers can include assessment of pinprick sensation (10) and reflexes. In individuals with significant early progressive symptoms of neuropathy or in whom a clinical suspicion of nondiabetic neuropathy exists, referral for additional neurologic evaluation is indicated.

MANAGEMENT OF NEUROPATHY

Intensive glycemic control is effective for primary prevention of or secondary intervention for neuropathy in people with type 1 diabetes (3,14,15). In those with type 2 diabetes, lower blood glucose levels are associated with reduced frequency of neuropathy (2,16). Multiple medications are available for effective management of neuropathic pain. There are insufficient comparative studies to justify a recommendation on which oral medication should be attempted first. Commonly available and commonly used tricyclic antidepressants (17,18), anticonvulsants (19,20) and opioid analgesics (21) are shown in Table 1. Combination therapy with gabapentin and opioid has been shown to achieve better analgesia at lower doses of each drug (22). Other antidepressants include desipramine (18) (a tricyclic antidepressant), venlafaxine (23), nortriptyline and fluphenazine (24), and duloxetine (25) (a dual reuptake inhibitor). Other opioid analgesics include tramadol (26) and sustained-release oxycodone (21); other anticonvulsants include carbamazepine (27), oxcarbazepine (28), lamotrigine (29) and topiramate (30). Alternate therapeutic options include topical isosorbide dinitrate (31) and the antiarrhythmic mexiletine (32). The efficacy of topical capsaicin is less clear (33,34).

Although subclinical autonomic neuropathic manifestations are common, symptomatic involvement is infrequent. The diagnosis of symptomatic autonomic neuropathy is based on exclusion of specific cardiovascular, gastrointestinal or genitourinary pathology, usually requiring assessment by a specialist in the affected system. Treatment of autonomic neuropathy is based primarily on expert opinion, but research in this field remains active.

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29

Foot Care, p. S143

Type 1 Diabetes in Children and Adolescents, p. S150

Type 2 Diabetes in Children and Adolescents, p. S162

Table 1. Oral medications for the management of neuropathic pain*			
Medication	Suggested starting dose[†]	Suggested titration[†]	Common or serious side effects
Tricyclic antidepressants			
Amitriptyline (17,18)	10 mg QHS	Increase weekly by 10 mg/day to a maximum of 150 mg/day	Dry mouth Blurred vision Constipation Urinary retention Dizziness Drowsiness Cardiac arrhythmias (particularly in the elderly)
Anticonvulsants			
Gabapentin (19) [‡]	300 mg TID	Increase weekly by 300 mg/day to a maximum of 3600 mg/day	Dizziness Somnolence Ataxia Fatigue Peripheral edema
Pregabalin (20)	75 mg BID	May double weekly to a maximum of 300 mg BID	Weight gain Peripheral edema Dizziness Somnolence
Opioid analgesics[‡]			
Sustained-release oxycodone (21)	10 mg BID	Increase every 3 days by 10 mg to a maximum of 60 mg BID	Constipation Nausea Somnolence

*Clinically important outcomes in the clinical trial setting are generally defined by a 30 to 50% decrease in pain (as assessed by visual analogue scores). Few patients achieve complete pain relief in these clinical trials.

[†]Dose ranges are for adults and are generalized from clinical trials – smaller starting doses and slower titration schedules may be indicated. Optimal doses are the lowest doses required for maximum efficacy without significant side effects. Although required for some agents, dose adjustments for renal and liver dysfunction are not shown here. Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

[‡]Combination therapy with gabapentin and an opioid has been shown to achieve better analgesia at lower doses of each drug (22).

RECOMMENDATIONS

1. In people with type 2 diabetes, screening for peripheral neuropathy should begin at diagnosis of diabetes and occur annually thereafter. In people with type 1 diabetes, annual screening should commence after 5 years' post-pubertal duration of diabetes [Grade D, Consensus].
2. Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10-g monofilament or loss of sensitivity to vibration at the dorsum of the great toe [Grade A, Level 1 (10)].
3. People with diabetes should be treated with intensified glycemic control to prevent the onset and progression of neuropathy [Grade A, Level 1A, for type 1 diabetes (3,14); Grade B, Level 2 (16), for type 2 diabetes].
4. Antidepressants [Grade A, Level 1A (23,25)], anticonvulsants [Grade A, Level 1A (19,20,22,28)], opioid analgesics [Grade A, Level 1A (22)] and topical isosorbide dinitrate [Grade B, Level 2 (31)] should be considered alone or in combination for relief of painful peripheral neuropathy.

RELEVANT APPENDIX

Appendix 4: Rapid Screening for Diabetic Neuropathy

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Foot Care

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Foot problems are a major cause of morbidity and mortality in people with diabetes and contribute to increased healthcare costs.
- Management of foot ulceration requires an interdisciplinary approach that addresses glycemic control, infection, lower extremity vascular status and local wound care.
- Uncontrolled diabetes can result in immunopathy with a blunted cellular response to foot infection.

INTRODUCTION

Foot problems are a major cause of morbidity and mortality in people with diabetes and contribute to increased healthcare costs (1,2). The sequence of events leading to lower-extremity amputation is well known. In people with neuropathy (3) or peripheral vascular disease (4), minor trauma to the foot leads to skin ulceration, infection and ultimately gangrene, resulting in amputation (5-9). Foot complications are a major reason for admission to the hospital for people with diabetes, accounting for approximately 20% of all diabetes-related admissions in the North American population (7,8,10-12). After amputation of 1 limb, the prognosis for the contralateral limb is poor (13,14).

RISK ASSESSMENT AND PREVENTIVE CARE

A number of wound classification systems exist for documentation of diabetic foot ulcers. Of these, the University of Texas Diabetic Wound Classification System has been validated as a predictor of serious outcomes in patients with diabetes with foot ulcers (15) (Table 1).

Characteristics that have been shown to confer high risk of ulceration include previous ulceration, neuropathy, structural deformity and limited joint mobility, peripheral vascular disease and microvascular complications (16,17). Noninvasive assessments for peripheral arterial disease in diabetes include the use of the ankle-brachial index, determination of systolic toe pressure by photoplethysmography (measurement of the intensity of light reflected from the skin surface and the red cells below, which is indicative of arterial pulse flow in the arterioles of the respective area), transcutaneous oximetry (tcPO₂), and Doppler arterial-flow studies (18,19). The ankle-brachial index may be arti-

ficially high in some individuals with diabetes due to medial arterial-wall calcification in lower-extremity arteries (20). Iodinated contrast arteriography has provided the most definitive evaluation of peripheral atherosclerosis, but can precipitate renal failure in individuals with renal insufficiency. Advanced magnetic resonance angiography has been used as an alternative to iodinated contrast studies in people at risk for renal complications (21,22), although caution may be necessary in view of a possible association with the gadolinium-based contrast agents used in magnetic resonance angiography and the development of nephrogenic systemic fibrosis in individuals with poor renal function (23,24).

Prevention of amputations necessitates the use of various measures, including regular foot examination and evaluation of amputation risk, regular callus debridement, education, professionally fitted therapeutic footwear to reduce plantar pressure and accommodate foot deformities, and early detection and treatment of diabetic foot ulcers (10,25-28). Callus should be considered a sign of increased pressure and risk for ulceration (29). Foot examination should also include skin temperature assessment. Increased warmth is the first indicator of inflammation in an insensate foot and may be the first sign of acute Charcot neuroarthropathy as a complication of loss of protective sensation in the foot (30-

Table 1. University of Texas Diabetic Wound Classification System (15)

Stage	Grade			
	0	I	II	III
A (no infection or ischemia)	Pre- or postulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

32). In addition, an acute Charcot foot may be associated with erythema and swelling, with overall clinical characteristics very similar to cellulitis (33,34).

MANAGEMENT

Appropriate management can prevent or heal diabetic foot ulcers, thereby greatly reducing the amputation rate (6,9,10,25,26,35,36). All people with diabetes should be instructed on proper foot care (including smoking cessation strategies) (Appendix 5), should strive to reach recommended glycemic targets, and should receive early referrals to a healthcare professional trained in foot care management if problems occur (37).

Management of foot ulceration requires an interdisciplinary approach (38) that addresses glycemic control, infection, lower-extremity vascular status and local wound care (39).

Essentials of good wound care involve provision of an optimal wound environment, off-loading of the ulcer site, and, in nonischemic wounds, regular debridement of nonviable tissue. In general, wound dressings that maintain a moist wound environment should be selected (40) (Appendix 6). Expedient debridement may be performed with sharp instruments or biologically with medical-grade maggots (41,42).

Pressure offloading may be achieved with temporary footwear until the ulcer heals and the character of the foot stabilizes. Removable and irremovable cast-walkers and total-contact casting have demonstrated proven efficacy as pressure-reducing devices in plantar-surface ulcers (43-45). Although very effective in healing noninfected, nonischemic plantar-surface neuropathic ulcers, total-contact casting requires careful individual selection and personnel trained specifically in its application due to its potential for complications (46).

Infections that complicate diabetic foot ulcers occur frequently and may be imminently limb threatening (47). Surface cultures (as opposed to cultures of deeper tissues) of ulcers in people with diabetes have produced inconsistent results in determining the bacterial pathogens involved (48-50). Initial antibiotic therapy is typically empiric and broad spectrum, with subsequent antibiotics tailored to results from appropriate cultures. Studies to date do not clearly identify a particular antibiotic agent that is more efficacious in reducing amputation, accelerating ulcer healing or resolving infection (51). Uncontrolled diabetes can result in immunopathy with a blunted cellular response to infection. Up to 50% of patients with diabetes who have a significant limb infection may not have systemic signs of fever or leukocytosis at presentation (52). Deep infections require prompt surgical debridement in addition to appropriate antibiotic therapy (53).

In medically suitable individuals with peripheral arterial disease, distal limb revascularization has proven benefit in long-term limb salvage (54). Where bony foot deformities prevent fitting of appropriate footwear and/or offloading of pressure-related ulcers, consultation from a surgeon skilled in foot sur-

gery may be considered to address the deformity (55-57).

Hyperbaric oxygen therapy may be useful as an adjunct to systemic antibiotics in individuals with deep, long-standing, nonhealing foot infections, provided there is an adequate perfused capillary bed in the wound area (i.e. by measuring tcPO₂ response to 100% oxygen challenge). Few studies support its use in treating uncomplicated neuropathic or ischemic diabetic foot ulcers. There are no evidence-based criteria to select people for hyperbaric oxygen therapy and to predict their response (58).

RECOMMENDATIONS

1. In people with diabetes, foot examinations by both the individual and healthcare providers should be an integral component of diabetes management to decrease the risk of foot lesions and amputations [Grade B, Level 2 (26,37)], and should be performed at least annually and at more frequent intervals in those at high risk [Grade D, Consensus]. Assessment by healthcare providers should include structural abnormalities (e.g. range of motion of ankles and toe joints, callus pattern, bony deformities, skin temperatures), evaluation for neuropathy and peripheral arterial disease, ulcerations and evidence of infection [Grade D, Level 4 (9,50)].
2. People at high risk of foot ulceration and amputation should receive foot care education (including counselling to avoid foot trauma), professionally fitted footwear, smoking cessation strategies and early referrals to a healthcare professional trained in foot care management if problems occur [Grade B, Level 2 (37)].
3. Individuals who develop a foot ulcer should be managed by a multidisciplinary healthcare team with expertise in the management of foot ulcers to prevent recurrent foot ulcers and amputation [Grade C, Level 3 (38)].
4. Any infection in a diabetic foot must be treated aggressively [Grade D, Level 4 (53)].

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29

Neuropathy, p. S140

RELEVANT APPENDICES

Appendix 5: Diabetes and Foot Care: A Patient's Checklist

Appendix 6: Diabetic Foot Ulcers: Essentials of Management

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Erectile Dysfunction

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Erectile dysfunction (ED) affects approximately 34 to 45% of men with diabetes, has been demonstrated to negatively impact quality of life among those affected across all age strata, and may be the earliest sign of cardiovascular disease.
- All adult men with diabetes should be regularly screened for ED with a sexual function history.
- The current mainstays of therapy are phosphodiesterase type 5 inhibitors. They have been reported to have a major impact on erectile function and quality of life, and should be offered as first-line therapy to men with diabetes wishing treatment for ED.

INTRODUCTION

Erectile dysfunction (ED) affects approximately 34 to 45% of men with diabetes, and has been demonstrated to negatively impact quality of life among those affected across all age strata. Furthermore, studies indicate that 40% of diabetic men >60 years of age have complete ED (1-9). Among the diabetic population, risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia, androgen deficiency states (10) and cardiovascular disease (CVD) (5,7,11,12). ED as a marker of potential CV events has been reported by numerous investigators (13-20). Diabetic retinopathy has been shown to correlate with the presence of ED (5,7,21). Organic causes of ED include microvascular and macrovascular disease, and neuropathy. In addition, psychological or situational factors may cause or contribute to ED.

Compared with the general population, multiple studies have reported men with diabetes having higher rates of hypogonadism (10,22-24). Importantly, phosphodiesterase type 5 (PDE5) inhibitors appear to be less effective in hypogonadal states (23,25,26), where treatment of nonresponders to PDE5 with testosterone replacement is successful in roughly 50% of individuals. In addition, ED is a side effect of many drugs commonly prescribed to men with diabetes, such as some antihypertensives and antidepressants.

SCREENING

All adult men with diabetes should be regularly screened for ED with a sexual function history. Screening for ED in men

with type 2 diabetes should begin at diagnosis of diabetes. Validated questionnaires (e.g. International Index of Erectile Function [27,28] or Sexual Health Inventory for Men [29]) have been shown to be both sensitive and specific in determining the presence of ED and providing a means of assessing response to therapy.

TREATMENT

While no randomized clinical trials have demonstrated that interventions that improve glycemic control also reduce the incidence and progression of ED, the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study showed that intensive glycemic control was effective for primary prevention of and secondary intervention for neuropathy, a condition that can impair sensory feedback from the penis, leading to reduced erectile function (30-32). The current data still show that tight glycemic control does not reverse ED (33-35).

The current mainstays of therapy are PDE5 inhibitors. They have been reported to have a major impact on erectile function, quality of life, and should be offered as first-line therapy to men with diabetes wishing treatment for ED (36-41).

Evolving evidence supports the potential beneficial effects of PDE5 inhibitors on endothelial function and lower urinary tract symptoms. Contraindications for the use of PDE5 inhibitors include unstable angina or untreated cardiac ischemia and concomitant use of nitrates (42,43).

Referral to a specialist in ED should be offered to men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated. Second-line therapies (e.g. vacuum constriction devices, intracorporal injection therapy with prostaglandin E1 [PGE1] alone or in combination with papaverine and phentolamine [triple therapy], intraurethral therapy using PGE1) or third-line therapy (penile prosthesis) may be considered for these men (44).

EJACULATORY DISORDERS

Ejaculatory disorders are another common disorder of sexual function in men with diabetes, occurring in up to 32% (45). They range in scope from retrograde ejaculation, usually secondary to autonomic neuropathy with incomplete closure of the bladder neck during ejaculation, to premature or retarded ejaculation.

RECOMMENDATIONS

1. All adult men with diabetes should be regularly screened for ED with a sexual function history [Grade D, Consensus].
2. A PDE5 inhibitor should be offered as first-line therapy to men with diabetes with ED if there are no contraindications to its use [Grade A, Level 1A (36-43)].
3. Referral to a specialist in ED should be considered for eugonadal men who do not respond to PDE5 inhibitors, or for whom the use of PDE5 inhibitors is contraindicated [Grade D, Consensus].
4. Men with diabetes and ED who do not respond to PDE5 therapy should be investigated for hypogonadism [Grade D, Level 4 (22,23,25,26)].
5. Men with diabetes and ejaculatory dysfunction who wish fertility should be referred to a healthcare professional experienced in the treatment of ejaculatory dysfunction [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Screening for the Presence of Coronary Artery Disease, p. S99

Diabetes in the Elderly, p. S181

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Type 1 Diabetes in Children and Adolescents

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Suspicion of diabetes in a child should lead to immediate confirmation of the diagnosis and initiation of treatment to reduce the likelihood of diabetic ketoacidosis (DKA).
- Management of pediatric DKA differs from DKA in adults because of the increased risk for cerebral edema. Pediatric protocols should be used.
- Children should be referred for diabetes education and ongoing care to a diabetes team with pediatric expertise.

Unless otherwise specified, the term “child” or “children” is used for individuals 0 to 18 years of age, and the term “adolescent” for those 13 to 18 years of age.

INTRODUCTION

Diabetes mellitus is the most common endocrine disease and one of the most common chronic conditions in children. Type 2 diabetes and other types of diabetes, including genetic defects of beta cell function such as maturity-onset diabetes of the young (MODY), are increasing in frequency and should be considered when clinical presentation is atypical for type 1 diabetes. This section addresses those areas of type 1 diabetes management that are specific to children.

EDUCATION

Children with new-onset type 1 diabetes and their families require intensive diabetes education by an interdisciplinary pediatric diabetes healthcare (DHC) team to provide them with the necessary skills and knowledge to manage this disease. The complex physical, developmental and emotional needs of children and their families necessitate specialized care to ensure the best long-term outcomes (1). Education topics must include insulin action and administration, dosage adjustment, blood glucose (BG) and ketone testing, sick-day management and prevention of diabetic ketoacidosis (DKA), nutrition therapy, exercise, and prevention, detection, and treatment of hypoglycemia. Anticipatory guidance and lifestyle counselling should be part of routine care, especially during critical developmental transitions (e.g. upon school entry, beginning high school). Healthcare providers should regularly initiate discussions with children and their families about school, diabetes camp, psychological issues, substance abuse, driver's licence and career choices.

Children with new-onset diabetes who present with DKA require a short period of hospitalization to stabilize the associated metabolic derangements and to initiate insulin therapy. Outpatient education for well children with new-onset diabetes has been shown to be less expensive than inpatient education and associated with similar or slightly better outcomes when appropriate resources are available (2).

GLYCEMIC TARGETS

As improved metabolic control reduces both the onset and progression of diabetes-related complications in adults and adolescents with type 1 diabetes (3,4) aggressive attempts should be made to reach the recommended glycemic targets outlined in Table 1. However, clinical judgement is required to determine which children can reasonably and safely achieve these targets. Treatment goals and strategies must be tailored to each child, with consideration given to individual risk factors. Young age at diabetes onset (<7 years of age) has been associated with poorer cognitive function in many studies (5). Episodes of severe hypoglycemia have been associated with poorer cognitive function in some follow-up studies, while other studies have found chronic hyperglycemia in young children to be associated with poorer cognitive performance (6-8).

INSULIN THERAPY

Insulin therapy is the mainstay of medical management of type 1 diabetes. A variety of insulin regimens can be employed, but few have been studied specifically in children with new-onset diabetes. The choice of insulin regimen depends on many factors, including the child's age, duration of diabetes, family lifestyle, socioeconomic factors, and family, patient and physician preferences. Regardless of the insulin regimen used, all children should be treated to meet glycemic targets.

The honeymoon period, which can last up to 2 years post-diagnosis, is characterized by good glycemic control and low insulin requirements (<0.5 units/kg/day). At the end of this period, more intensive management may be required to continue meeting glycemic targets. Two methods of intensive diabetes management have been used: multiple daily injection (MDI) regimens and continuous subcutaneous insulin infusion (CSII, insulin pump therapy). CSII is safe and effective and can be initiated at any age (9). Most (10-13), but not all (14), randomized controlled trials (RCTs) of CSII in children

have failed to demonstrate an improvement in glycated hemoglobin (A1C) compared with MDI. However, almost all clinic-based studies of CSII in school-aged children and adolescents have shown a significant reduction in A1C with reduced hypoglycemia 12 to 24 months after initiation of CSII when compared to pre-CSII levels (15).

Most, but not all, pediatric studies of the extended long-acting insulin analogues detemir and glargine have demonstrated improved fasting BG levels and fewer episodes of nocturnal hypoglycemia with a reduction in A1C (16-18).

GLUCOSE MONITORING

Self-monitoring of blood glucose (SMBG) is an essential part of management of type 1 diabetes (19). Subcutaneous continuous glucose sensors have demonstrated good accuracy except when BG levels are in the hypoglycemic range (20-22). Continuous glucose sensors may be a useful tool for improving glycemic control in individuals on intensive therapy (23).

NUTRITION

All children with type 1 diabetes should receive counselling from a registered dietitian experienced in pediatric diabetes. Children with diabetes should follow a healthy diet, as recommended for children without diabetes in *Eating Well with Canada's Food Guide* (24). This involves consuming a variety of foods from the 4 food groups (grain products, vegetables and fruits, milk and alternatives, meat and alternatives). There is no evidence that one form of nutrition therapy is superior to another in attaining age-appropriate glycemic targets. Appropriate matching of insulin to carbohydrate content may allow increased flexibility and improved glycemic control (25,26), but the use of insulin to carbohydrate ratios is not required. The effect of protein and fat on glucose absorption must also be considered. Nutrition therapy should be individualized (based on the child's nutritional needs, eating habits, lifestyle, ability and interest) and must ensure normal growth

and development without compromising glycemic control. This plan should be evaluated regularly and at least annually.

HYPOGLYCEMIA

Hypoglycemia is a major obstacle for children with type 1 diabetes and can affect their ability to achieve glycemic targets. Significant risk of hypoglycemia often necessitates less stringent glycemic goals, particularly for younger children. Severe hypoglycemia should be treated with pediatric doses of intravenous (IV) dextrose in the hospital setting, or glucagon in the home setting. In children, the use of mini-doses of glucagon has been shown useful in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate. A dose of 20 µg per year of age up to a maximum of 150 µg is effective at treating and preventing hypoglycemia, with an additional doubled dose given if the BG has not increased in 20 minutes (27,28).

CHRONIC POOR METABOLIC CONTROL

Diabetes control may worsen during adolescence. Factors responsible for this deterioration include adolescent adjustment issues, psychosocial distress, intentional insulin omission and physiologic insulin resistance. A careful multidisciplinary assessment should be undertaken for every child with chronic poor metabolic control (e.g. A1C >10.0%) to identify potential causative factors such as depression and eating disorders and to identify and address barriers to improved control (29,30).

DKA

DKA occurs in 15 to 67% of children with new-onset diabetes and at a frequency of 1 to 10 episodes per 100 patient years in those with established diabetes (31). As DKA is the leading cause of morbidity and mortality in children with diabetes (32), strategies are required to prevent the development of DKA. In new-onset diabetes, DKA can be prevented

Table 1. Recommended glycemic targets for children and adolescents with type 1 diabetes

Age (years)	A1C (%)	Fasting/preprandial PG (mmol/L)	2-hour postprandial PG* (mmol/L)	Considerations
<6	<8.5	6.0–12.0	–	Extra caution is required to minimize hypoglycemia because of the potential association between severe hypoglycemia and later cognitive impairment
6–12	<8.0	4.0–10.0	–	Targets should be graduated to the child's age
13–18	≤7.0	4.0–7.0	5.0–10.0	Appropriate for most adolescents [†]

*Postprandial monitoring is rarely done in young children except for those on pump therapy for whom targets are not available

[†]In adolescents in whom it can be safely achieved, consider aiming toward normal PG range (i.e. A1C ≤6.0%, fasting/preprandial PG 4.0–6.0 mmol/L, and 2-hour postprandial PG 5.0–8.0 mmol/L)

A1C = glycated hemoglobin

PG = plasma glucose

through earlier recognition and initiation of insulin therapy. Public awareness campaigns about the early signs of diabetes have significantly reduced the frequency of DKA in new-onset diabetes (33). In children with established diabetes, DKA results from failing to take insulin or poor sick-day management. Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children with psychiatric disorders and those with difficult family circumstances (34). The frequency of DKA in established diabetes can be decreased with education and family support (35) as well as access to 24-hour telephone services for parents of children with diabetes (36,37).

Management of DKA

While most cases of DKA are corrected without event, 0.7 to 3.0% of pediatric cases are complicated by cerebral edema (CE) (38), which is associated with significant morbidity (21 to 35%) and mortality (21 to 24%) (39). In contrast, CE has rarely been reported in adults (34,39). Although the cause of CE is still unknown, several factors are associated with increased risk (Table 2) (40-43). A bolus of insulin prior to infusion is not recommended (44) since it does not offer any faster resolution of acidosis (45,46) and may contribute to CE (47). Recent evidence suggests early insulin administration (within the first hour of fluid replacement) may increase the risk for CE (48). Special caution should be exercised in young children with DKA and new-onset diabetes or a greater degree of acidosis and extracellular fluid volume (ECFV) depletion because of the increased risk of CE. Use of bedside criteria may allow earlier identification of patients who require treatment for CE (49). DKA should be managed according to published protocols for management of pediatric DKA (50) (Figure 1).

IMMUNIZATION

Historically, national guidelines have recommended influenza and pneumococcal immunization for children with type 1 diabetes (51-53). Currently, there is no evidence supporting increased morbidity or mortality from influenza or pneumococcus in children with type 1 diabetes (54,55). However,

the management of type 1 diabetes can be complicated by illness, thus requiring parental knowledge of sick-day management and increased attention during periods of illness. For this reason, parents may choose to immunize their children.

SMOKING PREVENTION AND CESSATION

Smoking is a significant risk factor for both macrovascular and microvascular complications of diabetes (56). Smoking prevention should be emphasized throughout childhood and adolescence.

CONTRACEPTION AND SEXUAL HEALTH COUNSELLING

Adolescents with diabetes should receive regular counselling about sexual health and contraception. Unplanned pregnancies should be avoided, as pregnancy in females with type 1 diabetes with suboptimal metabolic control results in higher risks of maternal and fetal complications (57).

PSYCHOLOGICAL ISSUES

Some children and their parents have adjustment problems soon after the diagnosis of diabetes (58,59). Although most resolve these problems within the first year after diagnosis, those who do not are at risk for poor adaptation to diabetes, including regimen adherence problems, poor glycemic control and continued psychosocial difficulties (60,61). Stress (general and diabetes-specific) (62), inadequate social and family support (63,64), inappropriate beliefs about the nature of diabetes (63) and poor coping skills (65) may have a negative impact on self-care behaviours and glycemic control.

The diagnosis of diabetes may precipitate or exacerbate existing psychological disorders (66). As quality of life and diabetes control may be adversely affected by the presence of comorbid psychological disorders and health complications (66), the identification of potential psychiatric conditions, such as depression, anxiety and eating disorders, is critical. All children with diabetes and their families should be regularly screened for symptoms of psychological distress (67,68) (See "Psychological Aspects of Diabetes," p. S82).

Eating disorders

Ten percent of adolescent females with type 1 diabetes meet the *Diagnostic and Statistical Manual of Mental Disorders (4th Edition)* criteria for eating disorders compared to 4% of their age-matched peers without diabetes (69). Furthermore, eating disorders are associated with poor metabolic control and earlier onset and more rapid progression of microvascular complications (70). Eating disorders should be suspected in those adolescent and young adult females who are unable to achieve and maintain metabolic targets especially when insulin omission is suspected. It is important to identify individuals with eating disorders because different management strategies are required to optimize metabolic control and prevent microvascular complications (71).

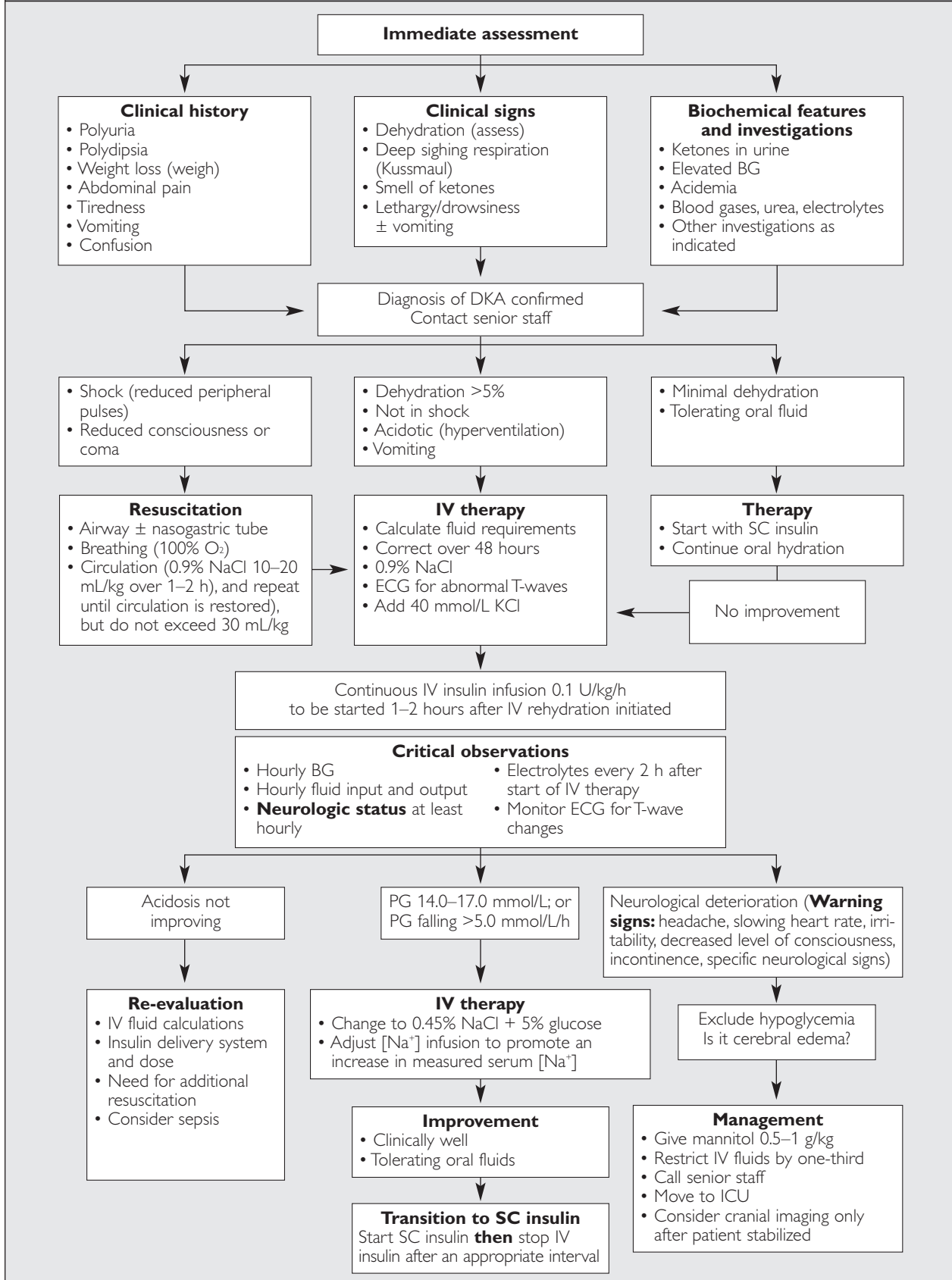
Table 2. Risks factors for CE

- Younger age (<5 years)
- New-onset diabetes
- High initial serum urea
- Low initial partial pressure of arterial carbon dioxide (pCO₂)
- Rapid administration of hypotonic fluids
- IV bolus of insulin
- Early IV insulin infusion (within first hour of administration of fluids)
- Failure of serum sodium to rise during treatment
- Use of bicarbonate

CE = cerebral edema

IV = intravenous

Figure 1. Immediate assessment and management of DKA in children



BG = blood glucose

ECG = electrocardiogram

IV = intravenous

SC = subcutaneous

DKA = diabetic ketoacidosis

ICU = intensive care unit

PG = plasma glucose

Adapted with permission from Reference 50.

COMORBID CONDITIONS

Autoimmune thyroid disease

Clinical autoimmune thyroid disease (AITD) occurs in 15 to 30% of individuals with type 1 diabetes (72). The risk for AITD during the first decade of diabetes is directly related to the presence or absence of thyroid antibodies at diabetes diagnosis (73). Early detection and treatment of hypothyroidism will prevent growth failure and symptoms of hypothyroidism (Table 3).

Addison disease

Addison disease is rare, even in those with type 1 diabetes (74). Targeted screening is required in those with unexplained recurrent hypoglycemia and decreasing insulin requirements (Table 3).

Celiac disease

Celiac disease can be identified in 4 to 9% of children with type 1 diabetes (72), but in 60 to 70% of these children the disease is asymptomatic (silent celiac disease). Children with type 1 diabetes are at increased risk for classic or atypical celiac disease during the first 10 years of diabetes (75). There is good evidence that treatment of classic or atypical

celiac disease with a gluten-free diet improves intestinal and extra-intestinal symptoms (76) and prevents the long-term sequelae of untreated classic celiac disease (77). However, there is no evidence that untreated asymptomatic celiac disease is associated with short- or long-term health risks (78) or that a gluten-free diet improves health in these individuals (79). Thus, universal screening for and treatment of asymptomatic celiac disease remain controversial (Table 3).

DIABETES COMPLICATIONS

There are important age-related considerations regarding surveillance for diabetes complications and interpretation of investigations (Table 4).

Nephropathy

A first morning urine albumin to creatinine ratio (ACR) has high sensitivity and specificity for the detection of microalbuminuria (80,81). Although screening with a random ACR is associated with greater compliance than with a first morning sample, its specificity may be compromised in adolescents due to their higher frequency of exercise-induced proteinuria and benign postural proteinuria. Abnormal random ACRs require confirmation with a first morning ACR or timed urine collection.

Microalbuminuria is rare in prepubertal children, regardless of the duration of diabetes or metabolic control (82). Furthermore, the likelihood of transient or intermittent microalbuminuria is higher during the early peripubertal years (83). Individuals with transient or intermittent microalbuminuria may be at increased risk of progression to overt nephropathy (84). Abnormal screening results require confirmation and follow-up to demonstrate persistent abnormalities.

Treatment is indicated only for those adolescents with persistent microalbuminuria. One short-term RCT in adolescents demonstrated that angiotensin-converting enzyme (ACE) inhibitors were effective in reducing microalbuminuria compared to placebo (85). However, there are no long-term intervention studies assessing the effectiveness of ACE inhibitors or angiotensin II receptor antagonists in delaying progression to overt nephropathy in adolescents with microalbuminuria. Therefore, treatment of adolescents with persistent microalbuminuria is based on the effectiveness of treatments in adults with type 1 diabetes (86).

Retinopathy

Retinopathy is rare in prepubertal children with type 1 diabetes and in postpubertal adolescents with good metabolic control (87,88).

Neuropathy

When present, neuropathy is mostly subclinical in children (89). While prospective nerve conduction studies and autonomic neuropathy assessment studies have demonstrated increased prevalence of abnormalities over time (90), persistence of abnormalities is an inconsistent finding (91).

Table 3. Recommendations for screening for comorbid conditions in children with type 1 diabetes

Condition	Indications for screening	Screening test	Frequency
Autoimmune thyroid disease	All children with type 1 diabetes	Serum TSH level + thyroperoxidase antibodies	At diagnosis and every 2 years thereafter
	Positive thyroid antibodies, thyroid symptoms or goiter	Serum TSH level + thyroperoxidase antibodies	Every 6–12 months
Addison disease	Unexplained recurrent hypoglycemia and decreasing insulin requirements	8 AM serum cortisol + serum sodium and potassium	As clinically indicated
Celiac disease	Recurrent gastrointestinal symptoms, poor linear growth, poor weight gain, fatigue, anemia, unexplained frequent hypoglycemia or poor metabolic control	Tissue transglutaminase + immunoglobulin A levels	As clinically indicated

TSH = thyroid-stimulating hormone

Vibration and monofilament testing have suboptimal sensitivity and specificity in adolescents (92). With the exception of intensifying diabetes management to achieve and maintain glycemic targets, no other treatment modality has been studied in children and adolescents.

Dyslipidemia

Most children with type 1 diabetes should be considered at low risk for vascular disease associated with dyslipidemia. The exceptions are those with longer duration of disease, microvascular complications or other cardiovascular disease (CVD) risk factors including smoking, hypertension, obesity and/or family history of premature CVD (93). Dyslipidemia screening should be targeted at those >12 years of age and younger children with specific risk factors for dyslipidemia. Statin therapy has not been studied specifically in children with diabetes, and there is no evidence linking specific low-density lipoprotein cholesterol (LDL-C) cutoffs in children with diabetes with long-term outcomes. In pubertal children without diabetes but with familial hypercholesterolemia, statin therapy is safe and effective at lowering LDL-C levels, and attenuating progression of carotid intima-media thickness, a surrogate marker for future vascular disease (94).

Hypertension

Up to 16% of adolescents with type 1 diabetes have hypertension (95). Twenty-four-hour ambulatory blood pressure (BP) monitoring has been used to exclude white coat hypertension and to identify loss of diurnal systolic rhythm (nondippers) with nocturnal hypertension in some normotensive adolescents with type 1 diabetes (96). These abnormalities may be predictive of future microalbuminuria (96). However, the role of ambulatory BP monitoring in routine care remains uncertain. Children with type 1 diabetes and confirmed hypertension should be treated according to the guidelines for children without diabetes (97).

TRANSITION TO ADULT CARE

The change of physician or DHC team can have a major impact on disease management and metabolic control in the person with diabetes. Between 25 and 65% of young adults have no medical follow-up during the transition from pediatric to adult diabetes care services (98,99). Those with no follow-up are more likely to experience hospitalization for DKA during this period. Organized transition services may decrease the rate of loss of follow-up (100).

Table 4. Screening for diabetes complications, dyslipidemia and hyperglycemia in children with type 1 diabetes

Complication	Indications and intervals for screening	Screening method
Nephropathy	<ul style="list-style-type: none"> Yearly screening commencing at 12 years of age in those with duration of type 1 diabetes >5 years 	<ul style="list-style-type: none"> First morning (preferred) or random ACR Abnormal ACR requires confirmation at least 1 month later with a first morning ACR, and if abnormal, followed by timed, overnight or 24-hour split urine collections for albumin excretion rate Repeated sampling should be done every 3–4 months over a 12-month period to demonstrate persistence
Retinopathy	<ul style="list-style-type: none"> Yearly screening commencing at 15 years of age with duration of type 1 diabetes >5 years Screening interval can increase to 2 years if good glycemic control, duration of diabetes <10 years, and no retinopathy at initial assessment 	<ul style="list-style-type: none"> 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard); or Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or Digital fundus photography
Neuropathy	<ul style="list-style-type: none"> Postpubertal adolescents with poor metabolic control should be screened yearly after 5 years' duration of type 1 diabetes 	<ul style="list-style-type: none"> Question and examine for symptoms of numbness, pain, cramps and paresthesia, as well as skin sensation, vibration sense, light touch and ankle reflexes
Dyslipidemia	<ul style="list-style-type: none"> Delay screening post-diabetes diagnosis until metabolic control has stabilized Screen at 12 and 17 years of age <12 years of age: screen only those with BMI >95th percentile, family history of hyperlipidemia or premature CVD 	<ul style="list-style-type: none"> Fasting total cholesterol, high-density lipoprotein cholesterol, triglycerides, calculated low-density lipoprotein cholesterol
Hypertension	<ul style="list-style-type: none"> Screen all children with type 1 diabetes at least twice a year 	<ul style="list-style-type: none"> Use appropriate cuff size

ACR = albumin to creatinine ratio

BMI = body mass index

CVD = cardiovascular disease

RECOMMENDATIONS

Delivery of care

- All children with diabetes should have access to an experienced pediatric DHC team and specialized care starting at diagnosis [Grade D, Level 4 (1)].
- Children with new-onset type 1 diabetes who are medically stable should receive their initial education and management in an outpatient setting, providing appropriate personnel and daily telephone consultation service are available in the community [Grade B, Level 1A (2)].
- To ensure ongoing and adequate metabolic control, pediatric and adult diabetes care services should collaborate to prepare adolescents and young adults for the transition to adult diabetes care [Grade C, Level 3 (100)].
- In the home situation, severe hypoglycemia in an unconscious child >5 years of age should be treated with 1 mg of glucagon subcutaneously or intramuscularly. In children ≤5 years of age, a dose of 0.5 mg of glucagon should be given. The episode should be discussed with the diabetes healthcare team as soon as possible and consideration given to reducing insulin doses for the next 24 hours to avoid further severe hypoglycemia [Grade D, Consensus].
- Dextrose 0.5 to 1 g/kg should be given over 1 to 3 minutes to treat severe hypoglycemia with unconsciousness when IV access is available [Grade D, Consensus].

Glycemic targets

- Glycemic targets should be graduated with age (Table 1):
 - Children <6 years of age should aim for an A1C of <8.5% [Grade D, Consensus]. Extra caution should be used to minimize hypoglycemia because of the potential association in this age group between severe hypoglycemia and later cognitive impairment [Grade D, Level 4 (101)].
 - Children 6 to 12 years of age should aim for an A1C target of <8.0% [Grade D, Consensus].
 - Adolescents should aim for the same glycemic targets as adults [Grade A, Level 1A (4)].
- Children with persistently poor diabetes control (e.g. A1C >10%) should be referred to a tertiary pediatric diabetes team and/or mental health professional for a comprehensive interdisciplinary assessment [Grade D, Consensus]. Intensive family and individualized psychological interventions aimed at improving glycemic control should be considered to improve chronically poor metabolic control [Grade A, Level 1A (102,103)].

Insulin therapy

- Children with new-onset diabetes should be started on at least 2 daily injections of short-acting insulin or rapid-acting insulin analogues combined with an intermediate- or long-acting insulin [Grade D, Consensus].
- Insulin therapy should be assessed at each clinical encounter to ensure it still enables the child to meet A1C targets, minimizes the risk of hypoglycemia and allows flexibility in carbohydrate intake, daily schedule and activities [Grade D, Consensus]. This assessment should include consideration of:
 - Increased frequency of injections [Grade D, Consensus]
 - Change in the type of basal (long-acting analogue) and/or prandial (rapid-acting analogue) insulin [Grade B, Level 2 (17), for adolescents; Grade D, Consensus, for younger children].
 - Change to CSII therapy [Grade C, Level 3 (104)].

Hypoglycemia

- In children, the use of mini-doses of glucagon (20 µg per year of age to a maximum of 150 µg) should be considered in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate [Grade D, Level 4 (27)].

Diabetic ketoacidosis

- To prevent DKA in children with diabetes:
 - Targeted public awareness campaigns should be considered to educate parents and other caregivers (e.g. teachers) about the early symptoms of diabetes [Grade C, Level 3 (33)].
 - Comprehensive education and support services [Grade C, Level 3 (35)], as well as 24-hour telephone services [Grade C, Level 3 (36)], should be available for families of children with diabetes.
- DKA in children should be treated according to pediatric-specific protocols [Grade D, Consensus]. If appropriate expertise/facilities are not available locally, there should be immediate consultation with a centre with expertise in pediatric diabetes [Grade D, Consensus].
- In children in DKA, rapid administration of hypotonic fluids should be avoided [Grade D, Level 4 (41)]. Circulatory compromise should be treated with only enough isotonic fluids to correct circulatory inadequacy [Grade D, Consensus]. Restoration of ECFV should be extended over a 48-hour period with regular reassessments of fluid deficits [Grade D, Level 4 (41)].
- In children in DKA, IV insulin bolus should not be given; an IV infusion of short-acting insulin should be used at an initial dose of 0.1 units/kg/hour [Grade D, Level 4 (45)]. The insulin infusion should not be started until 1 hour after starting fluid replacement therapy [Grade D, Level 4 (48)].
- In children in DKA, the insulin infusion rate should be maintained until the plasma anion gap normalizes. Once PG reaches 14.0 to 17.0 mmol/L, IV glucose should be started to avoid hypoglycemia [Grade D, Consensus].
- In children in DKA, administration of sodium bicarbonate should be avoided except in extreme circulatory compromise, as this may contribute to CE [Grade D, Level 4 (40)].

Microvascular complications

- Prepubertal children and those in the first 5 years of diabetes should be considered at very low risk for microalbuminuria [Grade A, Level 1 (82,83)]. Screening for microalbuminuria should be performed annually commencing at 12 years of age in children with type 1 diabetes >5 years' duration [Grade D, Consensus].

RECOMMENDATIONS

18. Adolescents with type 1 diabetes should be screened for microalbuminuria with a first morning urine ACR (preferred) [Grade B, Level 2 (81)] or a random ACR [Grade D, Consensus]. Abnormal results should be confirmed [Grade B, Level 2 (105)] at least 1 month later with a first morning ACR, and if abnormal, followed by timed, overnight, or 24-hour split urine collections for albumin excretion rate [Grade D, Consensus]. Microalbuminuria should not be diagnosed in adolescents unless it is persistent as demonstrated by 3 consecutive timed collections obtained at 3- to 4-month intervals over a 12-month period [Grade D, Consensus].
 19. Adolescents with persistent microalbuminuria should be treated as per adult guidelines [Grade D, Consensus].
 20. Proliferative retinopathy should be considered rare in prepubertal children, and within the first 5 years of diagnosis of diabetes [Grade B, Level 2 (87,106)]. In children ≥ 15 years of age with type 1 diabetes, screening and evaluation for retinopathy by an expert professional should be performed annually starting 5 years after the onset of diabetes [Grade D, Consensus]. The screening interval can be increased to every 2 years in children with type 1 diabetes who have good glycemic control, duration of diabetes < 10 years, and no significant retinopathy (as determined by an expert professional) [Grade D, Consensus].
 21. Postpubertal children with type 1 diabetes of > 5 years' duration and poor metabolic control should be questioned about symptoms of numbness, pain, cramps and paresthesia, and examined for skin sensation, vibration sense, light touch and ankle reflexes [Grade D, Consensus].
- Comorbid conditions and other complications**
22. Children with type 1 diabetes who are < 12 years of age should be screened for dyslipidemia if they have other risk factors such as obesity (BMI > 95 th percentile for age and gender), and/or a family history of dyslipidemia or premature CVD. Routine screening for dyslipidemia should begin at 12 years of age, with repeat screening after 5 years [Grade D, Consensus].
 23. Children with type 1 diabetes and dyslipidemia should be treated as per lipid guidelines for adults with diabetes [Grade D, Consensus].
 24. All children with type 1 diabetes should be screened for hypertension at least twice annually [Grade D, Consensus].
 25. Children with type 1 diabetes and BP readings persistently above the 95th percentile for age should receive lifestyle counselling, including weight loss if overweight [Grade D, Level 4 (107)]. If BP remains elevated, treatment should be initiated based on recommendations for children without diabetes [Grade D, Consensus].
 26. Influenza immunization should be offered to children with diabetes as a way to avoid an intercurrent illness that could complicate diabetes management [Grade D, Consensus].
 27. Formal smoking prevention and cessation counselling should be part of diabetes management for children with diabetes [Grade D, Consensus].
 28. Adolescent females with type 1 diabetes should receive counselling on contraception and sexual health in order to avoid unplanned pregnancy [Grade D, Consensus].
 29. Adolescent females with type 1 diabetes have a 2-fold increased risk for eating disorders [Grade B, Level 2 (69)] and should be regularly screened using nonjudgemental questions about weight and shape concerns, dieting, binge eating and insulin omission for weight loss [Grade D, Consensus].
 30. Children with type 1 diabetes who have thyroid antibodies should be considered high risk for autoimmune thyroid disease [Grade C, Level 3 (73)]. Children with type 1 diabetes should be screened at diabetes diagnosis with repeat screening every 2 years using a serum TSH and thyroperoxidase antibodies [Grade D, Consensus]. More frequent screening is indicated in the presence of positive thyroid antibodies, thyroid symptoms, or goiter [Grade D, Consensus].
 31. Children with type 1 diabetes and symptoms of classic or atypical celiac disease (Table 3) should undergo celiac screening [Grade D, Consensus], and if confirmed, be treated with a gluten-free diet to improve symptoms [Grade D, Level 4 (76)] and prevent the long-term sequelae of untreated classic celiac disease [Grade D, Level 4 (77)]. Parents should be informed that the need for screening and treatment of asymptomatic (silent) celiac disease is controversial [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Self-management Education, p. S25
 Targets for Glycemic Control, p. S29
 Monitoring Glycemic Control, p. S32
 Insulin Therapy in Type 1 Diabetes, p. S46
 Hypoglycemia, p. S62
 Psychological Aspects of Diabetes, p. S82
 Type 2 Diabetes in Children and Adolescents, p. S162

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Type 2 Diabetes in Children and Adolescents

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Anticipatory guidance regarding healthy eating and active lifestyle is recommended to prevent obesity.
- Regular targeted screening for type 2 diabetes is recommended in children at risk.
- Children with type 2 diabetes should receive care in consultation with an interdisciplinary pediatric diabetes healthcare team.
- Early screening, intervention and optimization of glycemic control are essential, as onset of type 2 diabetes during childhood is associated with severe and early onset of microvascular complications.

Unless otherwise specified, the term "child" is used for individuals 0 to 18 years of age, and the term "adolescent" for those 13 to 18 years of age.

INTRODUCTION

Type 2 diabetes in children has increased in frequency in North America over the past 2 decades (1). Most of these children are from ethnic groups at high risk for type 2 diabetes, namely of Aboriginal, African, Hispanic or Asian descent. Limited Canadian prevalence data are available. The prevalence of type 2 diabetes in Canadian Aboriginal children 5 to 18 years of age is as high as 1%, with the highest prevalence in the Plains Cree of Central Canada (2,3). Data from the United States suggest a 10- to 30-fold increase in the number of children with type 2 diabetes over the past 10 to 15 years (4).

PREVENTION

Breastfeeding has been shown to reduce the risk of youth-onset type 2 diabetes in some populations (5).

Obesity is a major modifiable risk factor for the development of type 2 diabetes. In 2004, 18% of Canadian children and adolescents were overweight and 8% were obese (6). Studies on prevention of obesity in children are limited and have generally not been demonstrated to be successful (7). In obese children, standard lifestyle interventions in the form of dietary recommendations and regular clinic visits have been shown to have little benefit (7). However, lifestyle intervention trials that included dietary and exercise interventions, intensive counselling and family involvement have demonstrated long-term (5 to 10 years) weight maintenance (7).

The role of pharmacotherapy in the treatment of childhood

obesity is controversial, as there are few controlled trials and no long-term safety or efficacy data (8). Several studies suggest that lifestyle changes plus pharmacotherapy may act synergistically when lifestyle intervention is aggressively pursued (8). Orlistat may be considered to aid in weight reduction and weight maintenance when added to a regimen of lifestyle intervention in adolescents (9-11). Metformin, orlistat and sibutramine each have potential for short-term positive effects on weight, glycemia, insulin sensitivity and/or lipids, but no pediatric studies have been performed to assess prevention of diabetes or long-term complications. In addition, safety concerns exist for sibutramine and possibly orlistat. In obese adolescents with evidence of severe insulin resistance, pharmacologic therapy with metformin or orlistat should only be considered after a comprehensive evaluation of the child's metabolic status, family history, and review of lifestyle intervention. Due to a lack of data in prepubertal children, the use of antiobesity drugs should only be considered within the context of a supervised clinical trial. Bariatric surgery in adolescents should be limited to exceptional cases and be performed only by experienced teams.

SCREENING AND DIAGNOSIS

Although not proven in children, it is generally assumed that earlier diagnosis of diabetes will lead to interventions that will improve glycemia and reduce the related short- and long-term complications (12). Children with type 2 diabetes from high-risk ethnic groups (Hispanic, African and Asian) have been identified in school-based screening studies in the United States (1) and Japan (13), but most have been reported as part of case series (4).

Risk factors for the development of type 2 diabetes in children include history of type 2 diabetes in a first- or second-degree relative (14), being a member of a high-risk population (e.g. people of Aboriginal, Hispanic, South Asian, Asian or African descent) (1), overweight (14-17), impaired glucose tolerance (IGT) (18), polycystic ovary syndrome (PCOS) (19), exposure to diabetes in utero (20,21), acanthosis nigricans (1,22), hypertension and dyslipidemia (23), and nonalcoholic fatty liver disease (NAFLD) (24). Atypical antipsychotic medications may cause significant weight gain and insulin resistance in children (25). Neuropsychiatric disorders and use of neuropsychiatric medications are more common in obese children at diagnosis of type 2 diabetes

compared to the general pediatric population (26).

While a fasting plasma glucose (FPG) is the recommended routine screening test for children, the oral glucose tolerance test (OGTT) may have a higher detection rate (15,27) in children who are very obese (body mass index [BMI] ≥ 99 th percentile for age and gender) and who have multiple risk factors for type 2 diabetes. An OGTT may also be more sensitive in less obese children who have multiple risk factors.

The diagnostic criteria for diabetes in children are the same as for adults.

CLASSIFICATION

In most children, the presence of clinical risk factors, mode of presentation and early course of the disease indicate whether the child has type 1 or type 2 diabetes. However, differentiation may be difficult in some. Children with type 2 diabetes can present with diabetic ketoacidosis (DKA) (28,29). Testing for the absence of islet autoantibodies may be useful (30-32). Fasting insulin levels are not helpful at diagnosis, as levels may be low due to glucose toxicity (33). DNA diagnostic testing for genetic defects in beta cell function should be considered in children who have a strong family history suggestive of autosomal-dominant inheritance and who are lacking features of insulin resistance. This may be helpful when diabetes classification is unclear, and may lead to more appropriate management (34,35).

MANAGEMENT

Children with type 2 diabetes should receive care in conjunction or consultation with an interdisciplinary pediatric diabetes healthcare team. To be effective, treatment programs for adolescents with type 2 diabetes need to address the lifestyle and health habits of the entire family, emphasizing healthy eating and physical activity (36). In addition, psychological issues, such as depression, self-destructive behaviour patterns and smoking cessation, need to be addressed and interventions offered as required. In Aboriginal children, lifestyle intervention has improved glycemic control to within the normal range in <2 weeks (37). Insulin is required in those with severe metabolic decompensation at diagnosis (e.g. DKA, glycated hemoglobin [A1C] $\geq 9.0\%$, symptoms of severe hyperglycemia), but may be successfully weaned once glycemic targets are achieved, particularly if lifestyle changes are effectively adopted (38). There are limited data about the safety or efficacy of oral antihyperglycemic agents in the pediatric population. Metformin has been shown to be safe in adolescents for up to 16 weeks, reducing A1C by 1.0 to 2.0% and lowering FPG with similar side effects as seen in adults (39).

IMMUNIZATION

The recommendations for influenza and pneumococcal immunization in Canada do not address the issue of type 2 diabetes in children, and there are no studies evaluating the usefulness of the influenza or pneumococcal vaccine in this population.

There is no reason not to manage these children in a similar fashion to those with type 1 diabetes. Some children with type 2 diabetes may, however, have other factors (e.g. Aboriginal heritage) that may place them at higher risk of increased influenza- and pneumococcal-related morbidity (40,41).

COMPLICATIONS

Short-term complications of type 2 diabetes in children include DKA and hyperglycemic hyperosmolar state (HHS). High morbidity and mortality rates have been reported in youth presenting with combined DKA and HHS at onset of type 2 diabetes (42-44).

Evidence suggests that early-onset type 2 diabetes in adolescence is associated with severe and early-onset microvascular complications (including retinopathy, neuropathy, nephropathy) (12,45,46). Although neither retinopathy nor neuropathy has been described in adolescents with type 2 diabetes at diagnosis, 1 study found that 1 in 5 youth with type 2 diabetes had peripheral nerve abnormalities and more than half had autonomic neuropathy after a median duration of diabetes of 1.3 years (46). Therefore, it is prudent to consider screening for these complications at diagnosis and yearly thereafter until the natural history is better understood (Table 1). As well, Aboriginal youth in Canada are at increased risk of renal diseases not associated with diabetes (47). Given that the documentation of persistent albuminuria may indicate 1 of several possible diagnoses, including underlying primary renal disease, diabetic nephropathy or focal sclerosing glomerulosclerosis (a comorbid condition associated with obesity), referral to a pediatric nephrologist for assessment of etiology and treatment is recommended.

COMORBID CONDITIONS

Children with type 2 diabetes have an increased prevalence of dyslipidemia (46,48). Screening for dyslipidemia at diagnosis and every 1 to 3 years as clinically indicated thereafter is recommended. In children with familial dyslipidemia and a positive family history of early cardiovascular events, a statin should be started if the low-density lipoprotein cholesterol level remains >4.2 mmol/L after a 3- to 6-month trial of dietary intervention (49). A similar approach seems reasonable in the absence of evidence to recommend a specific intervention in children with type 2 diabetes.

Similarly, as up to 36% of adolescents with type 2 diabetes have hypertension (46), screening should begin at diagnosis of diabetes and continue at every diabetes-related clinical encounter thereafter (50). (See "Type 1 Diabetes in Children and Adolescents," p. S150, for additional discussion on treatment of dyslipidemia and hypertension.)

Since most adolescents with type 2 diabetes show clinical evidence of obesity and insulin resistance, surveillance should occur for comorbid complications associated with insulin resistance, including PCOS (51) and NAFLD (52) (Table 1).

Table 1. Screening for diabetes complications and comorbidities in children with type 2 diabetes

Complication/ Comorbid condition	Indications and intervals for screening	Screening test
Dyslipidemia	Screening should commence at diagnosis of diabetes and every 1–3 years thereafter as clinically indicated	Fasting TC, HDL-C, TG, calculated LDL-C
Hypertension	At diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least twice annually)	BP measurement using appropriate size cuff
NAFLD	Yearly screening commencing at diagnosis of diabetes	ALT
Nephropathy	Yearly screening commencing at diagnosis of diabetes	<ul style="list-style-type: none"> • First morning (preferred) or random ACR • Abnormal ACR requires confirmation at least 1 month later with a first morning ACR and if abnormal, follow-up with timed, overnight or 24-hour split urine collections for albumin excretion rate • Repeated sampling should be done every 3–4 months over a 6- to 12-month period to demonstrate persistence
Neuropathy	Yearly screening commencing at diagnosis of diabetes	<p>Questioned and examined for:</p> <ul style="list-style-type: none"> • symptoms of numbness, pain, cramps, and paresthesia • skin sensation • vibration sense • light touch, and • ankle reflexes
PCOS	Yearly screening commencing at puberty in females with oligo/amenorrhea, acne and/or hirsutism	Androgen levels, including DHEAS and free testosterone
Retinopathy	Yearly screening commencing at diagnosis of diabetes	<ul style="list-style-type: none"> • 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard); or • Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or • Digital fundus photography

ACR = albumin to creatinine ratio

ALT = alanine aminotransferase

BP = blood pressure

DHEAS = dehydroepiandrosterone sulfate

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

NAFLD = nonalcoholic fatty liver disease

PCOS = polycystic ovary syndrome

TC = total cholesterol

TG = triglycerides

RECOMMENDATIONS

1. Anticipatory guidance promoting healthy eating, the maintenance of a healthy weight and regular physical activity is recommended as part of routine pediatric care [Grade D, Consensus].
2. Intensive lifestyle intervention, including dietary and exercise interventions, family counselling and family-oriented behaviour therapy, should be undertaken for obese children in order to achieve and maintain a healthy body weight [Grade D, Consensus].
3. Children 10 years of age, or younger if puberty is established, should be screened for type 2 diabetes every 2 years using an FPG test if they have ≥ 2 of the following risk factors [Grade D, Consensus]:
 - Obesity (BMI ≥ 95 th percentile for age and gender)
 - Member of high-risk ethnic group and/or family history of type 2 diabetes and/or exposure to diabetes in utero
 - Signs or symptoms of insulin resistance (including acanthosis nigricans, hypertension, dyslipidemia, NAFLD)
 - IGT
 - Use of antipsychotic medications/atypical neuroleptics
4. Very obese children (BMI ≥ 99 th percentile for age and gender) who meet the criteria in recommendation 3 should have an OGTT performed annually [Grade D, Consensus].
5. Commencing at the time of diagnosis of type 2 diabetes, all children should receive intensive counselling, including lifestyle modification, from an interdisciplinary pediatric healthcare team [Grade D, Consensus].
6. The target A1C for most children with type 2 diabetes should be $\leq 7.0\%$ [Grade D, Consensus].
7. In children with type 2 diabetes and an A1C $\geq 9.0\%$, and in those with severe metabolic decompensation (e.g. DKA), insulin therapy should be initiated, but may be successfully weaned once glycemic targets are achieved, particularly if lifestyle changes are effectively adopted [Grade D, Level 4 (38)].
8. In children with type 2 diabetes, if glycemic targets are not achieved within 3 to 6 months using lifestyle modifications alone, 1 of the following should be initiated: metformin [Grade B, Level 2 (39)] or insulin [Grade D, Consensus]. Metformin may be used at diagnosis in those children presenting with an A1C $>7.0\%$ [Grade B, Level 2 (39)].
9. Children with type 2 diabetes should be screened annually for microvascular complications (nephropathy, neuropathy, retinopathy) beginning at diagnosis of diabetes [Grade D, Level 4 (46)].
10. All children with type 2 diabetes and persistent albuminuria (2 abnormal of 3 samples over a 6- to 12-month period) should be referred to a pediatric nephrologist for assessment of etiology and treatment [Grade D, Consensus].
11. Children with type 2 diabetes should have a fasting lipid profile measured at diagnosis of diabetes and every 1 to 3 years thereafter as clinically indicated [Grade D, Consensus].
12. Children with type 2 diabetes should be screened for hypertension beginning at diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least biannually) [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories, p. S10
 Screening for Type 1 and Type 2 Diabetes, p. S14
 Prevention of Diabetes, p. S17
 Hyperglycemic Emergencies in Adults, p. S65
 Dyslipidemia, p. S107
 Treatment of Hypertension, p. S115
 Retinopathy, p. S134
 Type 1 Diabetes in Children and Adolescents, p. S150
 Type 2 Diabetes in Aboriginal Peoples, p. S187

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Diabetes and Pregnancy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

Pregestational diabetes

- All women with pre-existing type 1 or type 2 diabetes should receive preconception care to optimize glycemic control, assess complications, review medications and begin folate supplementation.
- Care by an interdisciplinary diabetes healthcare team composed of diabetes nurse educators, dietitians, obstetricians and endocrinologists, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with pre-existing type 1 or type 2 diabetes.

Gestational diabetes mellitus (GDM)

- The suggested screening test for GDM is the Gestational Diabetes Screen – a 50-g glucose load followed by a plasma glucose test measured 1 h later.
- Untreated GDM leads to increased maternal and perinatal morbidity, while intensive treatment is associated with outcomes similar to control populations.

INTRODUCTION

This chapter covers both pregnancy in pre-existing diabetes (pregestational diabetes) and gestational diabetes; as outlined in the text that follows, some of the management principles are common to all types of diabetes in pregnancy, including monitoring and lifestyle factors.

Blood glucose targets during pregnancy

Normal maternal blood glucose (1) and glycated hemoglobin (A1C) (2) levels during pregnancy are considerably lower than in nonpregnant adults: fasting and preprandial (mean±SD) 4.3±0.7 mmol/L; 1h postprandial 6.1±0.9 mmol/L; 2h postprandial 5.4±0.6 mmol/L; and 24-h mean 5.3 mmol/L. Values are higher in obese women (1).

While there is uncertainty about the precise levels of maternal plasma glucose (PG) required to prevent complications, there appears to be a glycemic threshold that identifies the majority of fetuses at risk. A mean PG <6.0 mmol/L is associated with a lower incidence of macrosomia, while rates of other complications increase at higher PG levels (3). Even in women without diabetes, fetal abdominal circumference correlates with postprandial PG levels (4). Current treatment of diabetes in pregnancy often results in higher mean

blood glucose levels than those in nondiabetic pregnancy (5). Recommended glycemic targets for preconception and during pregnancy are shown in Table 1.

Table 1. Recommended glycemic targets for preconception and during pregnancy*

Pre-pregnancy A1C	≤7.0%*
During pregnancy	
Fasting and preprandial PG	3.8–5.2 mmol/L
1h postprandial PG	5.5–7.7 mmol/L
2h postprandial PG	5.0–6.6 mmol/L
A1C	≤6.0% (normal)

*A1C ≤6.0% if this can be safely achieved. In some women, particularly those with type 1 diabetes, higher targets may be necessary to avoid excessive hypoglycemia

A1C = glycated hemoglobin

PG = plasma glucose

PREGESTATIONAL DIABETES

Recent large studies of women with pregestational diabetes continue to show higher rates of complications compared to the general population, including perinatal mortality, congenital malformations, hypertension, preterm delivery, large-for-gestational-age infants, cesarean delivery and neonatal morbidities (6-20). Adverse outcomes in pregnancies in women with type 2 diabetes, including congenital anomalies (8) and perinatal mortality (6), may be worse than in those with type 1 diabetes and may have actually increased over the past decade (9,21).

Preconception care

Preconception care for women with pregestational diabetes is associated with better outcomes, but <50% of women receive such care, and it is less common in women with type 2 diabetes (8,14). Higher A1C levels are associated with poorer outcomes (14), but even women who achieve tight glycemic control (A1C <7.0%) have an increased rate of complications (16). By discussing pregnancy prior to conception, healthcare providers may be able to improve out-

comes by educating women about the importance of strict glycemic control and encouraging them to participate in pre-pregnancy care.

Assessment and management of complications

Retinopathy

Women with type 1 (22,23) and type 2 diabetes (24) should have ophthalmologic assessments before conception, during the first trimester, as needed during pregnancy and within the first year postpartum (25). The risk of progression of retinopathy is increased with poor glycemic control during pregnancy, and such progression may occur up to 1 year postpartum (24,25). Additional risk factors for retinopathy progression include chronic and pregnancy-induced hypertension, pre-eclampsia and more severe pre-existing retinopathy (22,26-28). Pregnancy does not affect the long-term outcome of mild to moderate retinopathy (25).

Hypertension

The incidence of hypertension complicating pregnancy is 40 to 45% in women with type 1 and type 2 diabetes (28). Type 1 diabetes is more often associated with pre-eclampsia; type 2 diabetes with chronic hypertension. Of the risk factors for hypertension, poor glycemic control in early pregnancy is potentially modifiable. Some (29,30) but not all (31) studies have found that increased urinary protein excretion in early pregnancy raises the risk of developing hypertension.

Any type of hypertension is strongly associated with adverse outcomes. A number of antihypertensive medications are known to be safe and effective in pregnancy, including calcium channel blockers, beta-blockers, labetalol, hydralazine and methyldopa (32).

Chronic kidney disease

Prior to conception, women should be screened for chronic kidney disease (CKD) according to the guidelines (see "Chronic Kidney Disease in Diabetes," p. S126). In the presence of early CKD, monitoring of renal function using a random albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) from serum creatinine should occur each trimester. Microalbuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications (33-37). Proteinuria increases during pregnancy, but in women with a normal GFR, pregnancy has no adverse effects on long-term renal function as long as blood pressure and blood glucose are well controlled (33-36,38). In women with elevated serum creatinine, however, pregnancy can lead to a permanent deterioration in renal function (39,40).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are associated with an increased risk of congenital malformations and fetopathy, and their use should be avoided throughout pregnancy (41,42).

Cardiovascular disease

Although rare, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes. Myocardial infarction in pregnancy is associated with poor maternal and fetal outcomes (43,44). Women with known CVD should be evaluated and counselled about the significant risks associated with pregnancy.

Management

Care by an interdisciplinary diabetes healthcare (DHC) team composed of diabetes nurse educators, dietitians, obstetricians and endocrinologists, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with diabetes (20,45-47). An early working relationship should be established between the woman and DHC team to optimize care, facilitate planning of pregnancy, ensure adequate self-care practices and discuss the need for social support during pregnancy.

Women should begin supplementing their diet with multivitamins containing 5 mg folic acid at least 3 months pre-conception and continue until 12 weeks postconception. From this time and continuing through the pregnancy, the first 6 weeks postpartum and as long as breastfeeding continues, supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid (48).

Glycemic control

Hyperglycemia has adverse effects on the fetus throughout pregnancy: at conception and during the first trimester, it increases the risk of fetal malformations; later in pregnancy, it increases the risk of macrosomia and metabolic complications at birth (49). As a result, meticulous glycemic control is required for optimal maternal and fetal outcomes. Glycemic targets recommended for pregnancy are outlined in Table 1 (1,3,45,50-52).

During pregnancy there is a blunting of the normal counter-regulatory hormone responses to hypoglycemia (53,54). This and the risk of recurrent hypoglycemic episodes as a result of striving to reach glycemic targets may lead to hypoglycemia unawareness. Women with type 1 diabetes may, therefore, be at high risk of severe hypoglycemia, especially during the first trimester before relative insulin resistance from the placental hormones develops, and care should be taken to counsel these patients about the risks. There do not appear to be significant adverse effects on the neonate from maternal hypoglycemia (55); however, in the presence of hypoglycemia unawareness, there may be an increased risk of macrosomia related to erratic glycemic control, as well as an increased risk of maternal seizures (56,57).

Monitoring

Self-monitoring of blood glucose (SMBG) is essential during pregnancy (6). Both preprandial and postprandial testing are recommended to guide therapy in order to achieve glycemic

RECOMMENDATIONS

1. Women with type 1 or type 2 diabetes of reproductive age should:
 - a. Use reliable birth control if sexually active and if glycemic control is not optimal [Grade D, Consensus].
 - b. Be counselled about the necessity of pregnancy planning, including the importance of good glycemic control and the need to stop potentially embryopathic drugs prior to pregnancy [Grade D, Consensus].
2. Before attempting to become pregnant, women with type 1 or type 2 diabetes should:
 - a. Receive preconception counselling regarding optimal diabetes management and nutrition, preferably in consultation with an interdisciplinary pregnancy team, to optimize maternal and neonatal outcomes [Grade C, Level 3 (47,88,89)].
 - b. Strive to attain a preconception A1C $\leq 7.0\%$ ($<6.0\%$ if safely achievable) to decrease the risk of:
 - Spontaneous abortions [Grade C, Level 3 (90), for type 1 diabetes; Grade D, Consensus, for type 2 diabetes]
 - Congenital malformations [Grade C, Level 3 (47,91,92)]
 - Pre-eclampsia [Grade C, Level 3 (93,94)]
 - Progression of retinopathy in pregnancy [Grade A, Level 1A (24), for type 1 diabetes; Grade D, Consensus, for type 2 diabetes].
 - c. Supplement their diet with multivitamins containing 5 mg folic acid at least 3 months preconception and continuing until at least 12 weeks postconception [Grade D, Consensus]. From 12 weeks postconception and throughout the pregnancy, the first 6 weeks postpartum and as long as breastfeeding continues, supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid [Grade D, Consensus].
 - d. Discontinue medications considered to be potentially embryopathic, including any from the following classes:
 - ACE inhibitors and ARBs [Grade C, Level 3 (42)]. In the setting of hypertension, these may be replaced with antihypertensives that are known to be safe in pregnancy (calcium channel blockers, beta-blockers, labetalol, hydralazine and methyldopa) [Grade D, Consensus].
 - Statins [Grade D, Level 4 (95)].
 - e. Undergo an ophthalmologic evaluation by an eye care specialist. Repeat assessments should be performed during the first trimester, as needed during the rest of pregnancy and within the first year postpartum [Grade A, Level 1, for type 1 diabetes (24,96); Grade D, Consensus, for type 2 diabetes].
3. Women with type 2 diabetes who are planning a pregnancy or become pregnant should:
 - a. Switch from oral antihyperglycemic agents to insulin [Grade D, Consensus]. This should preferably be done prepregnancy, except in the setting of PCOS, where metformin can be safely used for ovulation induction [Grade D, Consensus]. The safety of metformin beyond ovulation induction in women with type 2 diabetes remains unknown [Grade D, Consensus].
 - b. Receive an individualized insulin regimen to achieve glycemic targets, with consideration given to intensive insulin therapy [Grade A, Level 1 (65)].
4. Pregnant women with type 1 or type 2 diabetes should:
 - a. Strive to achieve target glucose values:
 - Fasting/preprandial PG: 3.8 to 5.2 mmol/L
 - 1h postprandial PG: 5.5 to 7.7 mmol/L
 - 2h postprandial PG I: 5.0 to 6.6 mmol/L
 - b. Perform SMBG, both pre- and postprandially (≥ 4 times/day if needed) to achieve glycemic targets and improve pregnancy outcomes [Grade C, Level 3 (47)].
 - c. Receive nutrition counselling from a registered dietitian who is part of the DHC team during pregnancy [Grade C, Level 3 (89)] and postpartum [Grade D, Consensus]. Recommendations for weight gain during pregnancy should be based on pregravid body mass index (BMI) [Grade D, Consensus].
 - d. Avoid ketosis during pregnancy [Grade C, Level 3 (97)].
5. Women with type 1 diabetes in pregnancy should receive intensive insulin therapy with multiple daily injections or an insulin pump to attain glycemic targets during pregnancy [Grade A, Level 1A (20,65)].

Postpartum

6. Women with type 1 diabetes in pregnancy should be screened for postpartum thyroiditis with a thyroid-stimulating hormone test at 6 weeks postpartum [Grade D, Consensus].

targets (50). Due to the increased risk of nocturnal hypoglycemia during pregnancy, testing during the night is often necessary in patients receiving insulin (56). Because starvation ketosis is common in pregnancy and may have detrimental effects on the fetus, urine and/or blood monitoring of ketones is warranted to confirm that the diet is adequate (58,59).

Lifestyle

During pregnancy, women should be evaluated and followed by a registered dietitian to ensure that nutrition therapy promotes euglycemia, appropriate weight gain and

adequate nutritional intake (60,61). Meal planning should emphasize moderate carbohydrate restriction and distribution over 3 meals and 3 snacks, 1 of which should be at bedtime. Hypocaloric diets are not recommended, as they result in weight loss and significant ketosis and are likely inadequate in required nutrients such as protein and calcium (62). Pre-pregnancy body mass is a potent predictor of birth weight and should be considered when making recommendations about energy intake and rate of weight gain (62). Physical activity should be encouraged, unless obstetrical contraindications exist or glycemic control is worsened by the activity (63).

Pharmacologic interventions

Insulin

Insulin therapy must be individualized and regularly adapted to the changing needs of pregnancy (20,46,50,64,65). Intensive insulin therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII or the insulin pump) is recommended to achieve glycemic targets prior to pregnancy. Women using CSII should be educated about the increased risk of diabetic ketoacidosis (DKA) in the event of insulin pump failure, because DKA is a potentially fatal complication for the fetus (66). Short-acting analogues aspart and lispro can be safely used in pregnancy (67-70). However, although aspart and lispro can help women achieve postprandial targets without severe hypoglycemia (71,72), no significant improvements in A1C or in fetal or maternal outcomes have been demonstrated compared with regular insulin in pregnant women with pregestational diabetes (73). There is insufficient evidence on the use of detemir or glargine in pregnancy, but in women who cannot tolerate NPH because of nocturnal hypoglycemia, consideration may be given to the use of detemir following a discussion of the risks and benefits. While there are case series of patients using glargine in pregnancy with no adverse effects (74), theoretical considerations would suggest that patients should avoid glargine use in pregnancy (75).

Oral antihyperglycemic agents and type 2 diabetes

A meta-analysis of first-trimester use of either glyburide or metformin did not show an increased incidence of congenital anomalies (76). However, studies have found increased perinatal mortality and pre-eclampsia in women treated with metformin and/or glyburide compared to those treated with insulin, despite similar glycemic control (77,78). As a result, oral agents are not recommended for glycemic control in women with type 2 diabetes during pregnancy.

Metformin and polycystic ovary syndrome

Women with polycystic ovary syndrome (PCOS), some of whom also had type 2 diabetes, have been treated with metformin to increase fertility and decrease miscarriage rates. Treatment of PCOS with metformin reduces testosterone levels and improves insulin levels and insulin resistance both before and during pregnancy (79,80). Although metformin crosses the placenta, 1 small study found no increase in the rate of congenital malformations, neonatal hypoglycemia or abnormal growth and motor development at 18 months (81).

Postpartum

Breastfeeding

All women should be encouraged to breastfeed, since this may reduce offspring obesity, especially in the setting of maternal obesity (82).

Few studies have examined breastfeeding and use of oral agents. Three case series (83-85) found metformin in the

milk and plasma of breastfeeding women who were taking metformin 500 mg BID or TID, but infant exposure was well below the 10% "level of concern" (0.18 to 0.65%). A study looking at weight, height and motor-social development up to 6 months of age in children of mothers taking metformin while breastfeeding showed normal development and no difference from formula-fed infants (81). One case series that looked at women taking glyburide or glipizide while breastfeeding found neither drug in the breast milk, and the maximum theoretical infant dose again was well below 10% (<1.5%), with no hypoglycemia found in the 3 infants tested (86). There are no studies to date looking at thiazolidinedione (TZD) use while breastfeeding. As a result, metformin and glyburide can be considered for use during breastfeeding, although further long-term studies are needed to better clarify the safety of these drugs.

Postpartum thyroiditis

Women with type 1 diabetes have a high risk of autoimmune thyroid disease (87) and should be screened for postpartum thyroiditis with a thyroid-stimulating hormone test at 6 weeks postpartum.

GESTATIONAL DIABETES MELLITUS

Definition and prevalence

Gestational diabetes mellitus (GDM) is defined as hyperglycemia with onset or first recognition during pregnancy (98). The prevalence of GDM is population-specific and reflects the underlying incidence of diabetes in that population (99). In Canada, the prevalence of GDM is higher than previously thought, varying from 3.7% in the non-Aboriginal (but probably multiethnic) population to 8–18% in Aboriginal populations (99-101).

Screening and diagnosis

Given conclusive evidence demonstrating that treatment of GDM is worthwhile (102), it is important to make the diagnosis of this generally asymptomatic condition. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was designed to determine whether hyperglycemia during pregnancy was associated with increased risk of maternal or fetal complications compared to overt diabetes. This large study (N=23 316) confirms that an increase in the glucose level during the oral glucose tolerance test (OGTT) of 1 standard deviation in pregnancy is associated with fetal hyperinsulinemia, increased birth weight, higher rates of cesarian deliveries and more neonatal hypoglycemia (103). However, the international approach to the diagnosis of GDM remains fragmented (104).

The suggested screening test is the Gestational Diabetes Screen (GDS) – a 50-g glucose load, with a PG measured 1 h later. The 2003 Canadian Diabetes Association guidelines (as well as these current guidelines) recommend diagnosing GDM if the glucose level 1 h after the GDS is ≥ 10.3 mmol/L.

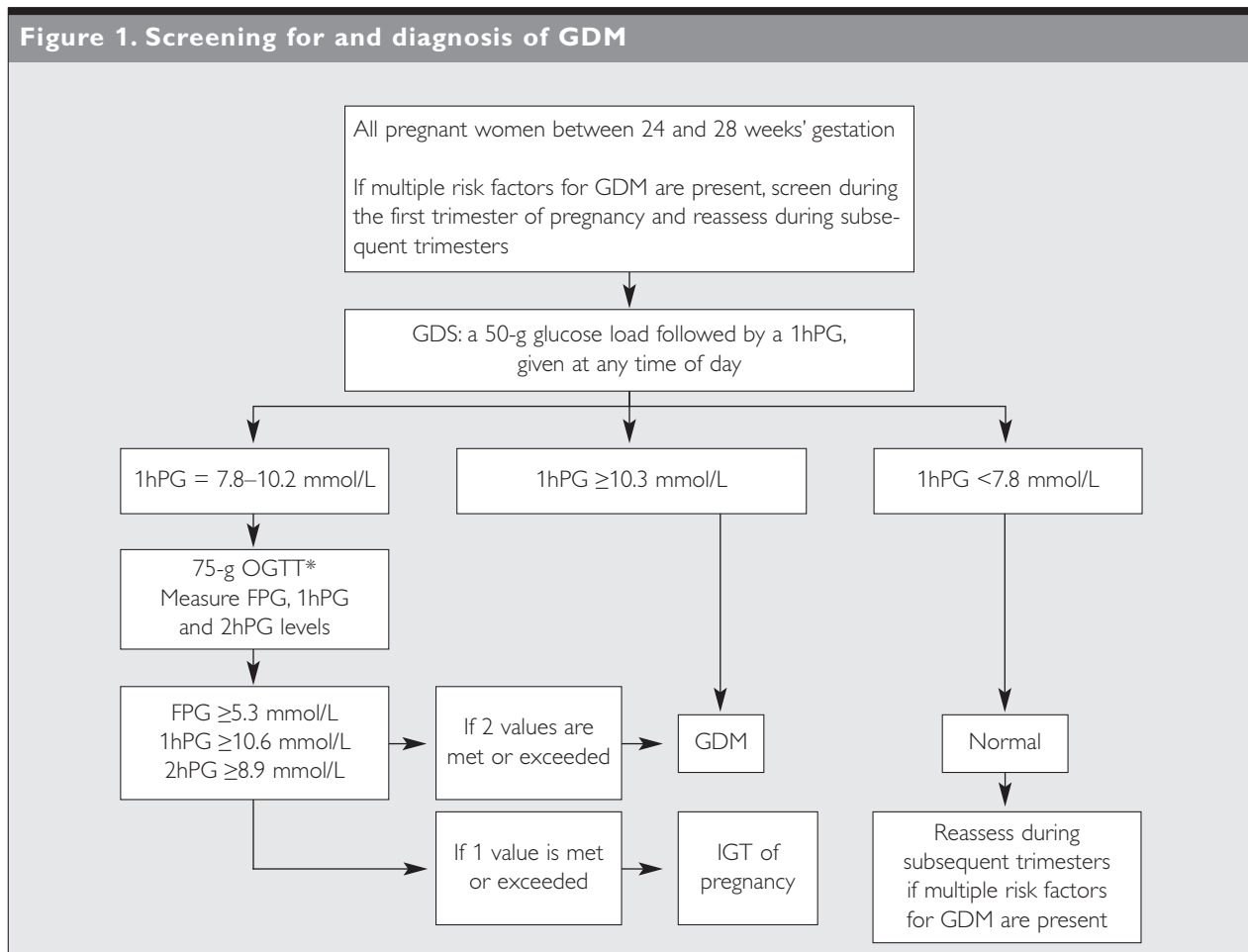
Continuing to use the cutoff of 10.3 mmol/L postscreen is reasonable to presume the presence of GDM. Retrospective studies published since the 2003 guidelines indicate a threshold of 11.1 mmol/L would give a false positive rate of 7% for GDM diagnosis (105) and be 79% predictive of GDM (106). There were increased cesarean delivery or shoulder dystocia rates once the screening result was ≥ 11.1 mmol/L, even if GDM was not diagnosed (106). A1C testing remains too insensitive (107), and the GDS is a better screening test than the FPG test (108). A large retrospective cohort study confirmed that the 7.8 mmol/L cutoff is valid for white people, but there are minor racial differences (109). These guidelines for diagnosing GDM are robust in terms of predicting macrosomia or the need for cesarian delivery (110). In the presence of a screening value of 7.8 to 10.2 mmol/L, a 75-g OGTT is indicated, with samples at 0, 1 and 2 h. Normal PG levels are fasting plasma glucose (FPG) < 5.3 mmol/L, 1-hour PG < 10.6 mmol/L and 2-hour PG < 8.9 mmol/L. If 2 of the 3 values are met or exceeded, a diagnosis of GDM is established. Two large retrospective studies found that 1 abnormal value on the OGTT had a worse outcome (111,112). Thus, if only 1 value is met or exceeded,

the diagnosis is impaired glucose tolerance (IGT) of pregnancy (see Figure 1).

All pregnant women should be screened for GDM between 24 and 28 weeks' gestation. Women with multiple risk factors should be screened during the first trimester (Figure 1). Risk factors include previous diagnosis of GDM or delivery of a macrosomic infant, member of a high-risk population (Aboriginal, Hispanic, South Asian, Asian, African), age ≥ 35 years, BMI ≥ 30 kg/m², PCOS, acanthosis nigricans and corticosteroid use. Universal screening is better than a risk factor-based approach; an observational study demonstrated a 2-fold increase in the rate of large-for-gestational-age neonates and their admission rate to the pediatric unit in the risk factor alone versus the universally screened group (113). Another study showed that a risk factor approach would miss half the cases of GDM (114). Both these studies confirm the findings of an earlier large prospective, randomized study (115).

An international consensus meeting is planned for the summer of 2008 with the goal of standardizing the criteria for diagnosing GDM; the guidelines for diagnosing GDM presented here will remain unaltered pending the outcome of that meeting.

Figure 1. Screening for and diagnosis of GDM



*In view of the controversies about diagnostic tests, other accepted methods may be used.

1hPG = 1-hour plasma glucose
2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose

GDM = gestational diabetes mellitus
GDS = Gestational Diabetes Screen

IGT = impaired glucose tolerance
OGTT = oral glucose tolerance test

Management

Untreated GDM (116) or IGT (102) leads to increased maternal and perinatal morbidity, while intensive treatment is associated with outcomes similar to control populations (52,117,118). Some women with GDM actually have undiagnosed type 2 diabetes, and this group has an increased risk of offspring having congenital malformations (101,119,120). Women at high risk of type 2 diabetes (advanced maternal age, strong family history, previous GDM, ethnic predisposition, marked obesity) should be assessed for diabetes at the first prenatal visit if this has not been done in the 6 months before pregnancy. The recommended glycemic targets (Table 1), use of SMBG and lifestyle interventions are similar for all types of diabetes in pregnancy. Since many women of different high-risk ethnic backgrounds have GDM, it is important to have culturally relevant educational materials available. Use of 1-hour or 2-hour postprandial glucose levels appears to be equally effective in therapy (121).

Monitoring

SMBG is essential during pregnancy (6). Both preprandial and postprandial testing are recommended to guide therapy in order to achieve glycemic targets (50,116). Due to the increased risk of nocturnal hypoglycemia during pregnancy, testing during the night is often necessary in patients receiving insulin (56). Because starvation ketosis is common in pregnancy and may have detrimental effects on the fetus, urine and/or blood monitoring of ketones is warranted to confirm that the diet is adequate (58,59).

Lifestyle

During pregnancy, women should be evaluated and followed by a registered dietitian to ensure that nutrition therapy promotes euglycemia, appropriate weight gain and adequate nutritional intake (60,61,122,123). Meal planning should emphasize moderate carbohydrate restriction and distribution over 3 meals and 3 snacks, 1 of which should be at bedtime. Hypocaloric diets are not recommended, as they result in weight loss and significant ketosis and are likely inadequate in required nutrients, such as protein and calcium. Pre-pregnancy body mass is a potent predictor of birth weight and should be considered when making recommendations about energy intake and rate of weight gain (62). Detailed recommendations for nutritional management of GDM are available (123). Physical activity should be encouraged unless obstetrical contraindications exist or glycemic control is worsened by the activity (63,124).

Pharmacologic interventions

Insulin

If women with GDM or IGT do not achieve glycemic targets within 2 weeks from nutrition therapy alone, insulin therapy should be initiated (125,126). In some cases, assessment of fetal growth by early third-trimester ultrasound can be used

to guide therapy (127,128). The use of insulin to achieve glycemic targets has been shown to reduce fetal and maternal morbidities (52,126). A variety of protocols can be used, with multiple injections being the most effective (65). Insulin usually needs to be continuously adjusted to achieve target glucose values. Although short-acting analogues aspart and lispro can help achieve postprandial glucose targets without severe hypoglycemia (71,72), improvements in fetal outcomes or in fetal growth parameters have not been demonstrated with the use of lispro compared to regular insulin in clinical trials in women with GDM (73).

Glyburide

Glyburide is safe and effective at controlling glucose levels in over 80% of patients with GDM (129-131) and does not cross the placenta (132). Women with higher fasting and postprandial glucose values on their OGTT (133), or while on diet therapy (132), are less likely to respond to glyburide. Despite good glucose levels, however, some studies report more adverse perinatal outcomes in women treated with glyburide than with insulin (134,135). Glyburide can be considered for women in whom insulin cannot be used.

Metformin

In a recent study (136), 751 women with GDM were randomly assigned to open treatment with metformin (with supplemental insulin if required) or insulin. Of the women assigned to metformin, 46.3% received supplemental insulin. Metformin (alone or with supplemental insulin) was not associated with increased perinatal complications compared with insulin. There was less severe hypoglycemia in neonates receiving metformin, but more spontaneous preterm delivery (i.e. <37 weeks' gestation). While metformin appears to be a safe alternative to insulin therapy, it does cross the placenta. Results of the offspring follow-up of the Metformin in Gestational Diabetes trial (MiG TOFU), expected in several years, will provide more data on its long-term safety.

As the use of metformin or glyburide during pregnancy is currently not an approved indication in Canada, such use would be considered off-label and would therefore require the appropriate discussion with patients.

Postpartum

Breastfeeding

All women should be encouraged to breastfeed, since this may reduce offspring obesity, especially in the setting of maternal obesity, and prevent the development of type 2 diabetes (82,137,138).

Long-term maternal risks

With the diagnosis of GDM, there is evidence of both impairment of insulin secretion and action (139,140). These defects persist postpartum and increase the risk of impaired fasting

glucose, IGT and type 2 diabetes (141,142). The cumulative incidence increases markedly in the first 5 years postpartum and more slowly after 10 years (143,144). At 3 to 6 months postpartum, risks of dysglycemia are in the 16 to 20% range, and the cumulative risks increase to a 30 to 60% range, depending on time since the index pregnancy and the population studied. The strongest predictor of early postpartum development of diabetes is elevated FPG during pregnancy (145,146).

Some women with GDM, especially lean women <30 years of age who require insulin during pregnancy, progress to type 1 diabetes (147,148). Women with positive autoantibodies (anti-GAD, IA-2) are more likely to have diabetes by 6 months postpartum (149).

Postpartum testing is essential to identify women who continue to have diabetes, those who develop diabetes after temporary normalization and those at risk, including those with IGT. However, many women do not receive adequate postpartum follow-up (150,151), and it is essential that the importance of follow-up be explicitly communicated with the woman

and her caregivers who are responsible for postpartum testing.

Women should be screened postpartum to determine their glucose status. Postnatal FPG has been the most consistently found variable in determining women at high risk for early postpartum diabetes (152). A FPG alone, however, will miss many women with some degree of abnormal glucose tolerance (153), and therefore, a 75-g OGTT should be done between 6 weeks and 6 months postpartum.

Metabolic syndrome has been shown to be more prevalent in women with GDM, especially those who are obese and non-Caucasian in some (154-156) but not all studies (157). Given the increased risk of CVD with metabolic syndrome, consideration should be given to screening for all components of metabolic syndrome in the postpartum care of women with GDM. Education on lifestyle modification to prevent diabetes and CVD should begin in pregnancy and continue postpartum. Emphasis on targeted strategies that incorporate women's exercise beliefs may increase participation rates (158) (see "Prevention of Diabetes," p. S17).

RECOMMENDATIONS

7. All pregnant women should be screened for GDM [Grade C, Level 3 (113,115)]. For most women, screening should be performed between 24 and 28 weeks' gestation [Grade D, Consensus]. Women with multiple risk factors should be screened during the first trimester and, if negative, should be reassessed during subsequent trimesters [Grade D, Consensus].
 8. Screening for GDM should be conducted using the GDS – a 50-g glucose load followed by a PG test measured 1 h later [Grade D, Level 4 (108)]. If GDM is strongly suspected, an OGTT can be performed without an initial GDS [Grade D, Consensus].
 9. Women who have a positive screening test (a 1hPG of 7.8 to 10.2 mmol/L on the GDS) should undergo an OGTT in order to diagnose GDM. A value of ≥ 10.3 mmol/L is considered diagnostic of GDM, in which case an OGTT does not need to be performed [Grade D, Consensus].
 10. GDM is diagnosed when at least 2 of the following values on the OGTT are met or exceeded. If 1 value is met or exceeded, a diagnosis of IGT of pregnancy is made [Grade D, Consensus]:
 - FPG: ≥ 5.3 mmol/L
 - 1hPG: ≥ 10.6 mmol/L
 - 2hPG: ≥ 8.9 mmol/L
 11. Women with GDM should:
 - a. Strive to achieve target glucose values:
 - Fasting/preprandial PG: 3.8 to 5.2 mmol/L
 - 1h postprandial PG: 5.5 to 7.7 mmol/L
 - 2h postprandial PG: 5.0 to 6.6 mmol/L
 - b. Perform SMBG both pre- and postprandially (≥ 4 times per day, if needed) to achieve glycemic targets and improve pregnancy outcomes [Grade C, Level 3 (47)].
 - c. Receive nutrition counselling from a registered dietitian during pregnancy [Grade C, Level 3 (89)] and postpartum [Grade D, Consensus]. Recommendations for weight gain during pregnancy should be based on pregravid BMI [Grade D, Consensus].
 - d. Avoid ketosis during pregnancy [Grade C, Level 3 (97)].
 12. If women with GDM do not achieve glycemic targets within 2 weeks using nutrition therapy alone, insulin therapy should be initiated [Grade D, Consensus], with up to 4 injections/day considered [Grade A, Level 1A (65)].
 13. Glyburide [Grade B, Level 2 (130,134,135)] or metformin [Grade B, Level 2 (136)] may be considered as second-line agents in women with GDM who are nonadherent to or who refuse insulin. Glyburide may be preferred, as metformin use is more likely to need supplemental insulin for glycemic control and metformin crosses the placenta with unknown long-term effects. Use of oral agents in pregnancy is off-label and should be discussed with the patient [Grade D, Consensus].
- Postpartum**
14. As women who have had GDM are defined as high risk of developing subsequent type 2 diabetes, they should be re-evaluated postpartum [Grade D, Consensus]. A 75-g OGTT should be performed between 6 weeks and 6 months postpartum to establish their glucose status. Women who are suspected of having had pre-existing diabetes should be monitored more closely postpartum. All women with GDM should be counselled on a healthy lifestyle.
 15. Women with previous GDM should follow the screening and prevention guidelines for other high-risk groups screened for type 2 diabetes [Grade D, Consensus] and should be screened for type 2 diabetes when planning another pregnancy [Grade D, Consensus].

Long-term risks in offspring

There is compelling evidence that offspring exposed to GDM are at increased risk of obesity and IGT, especially if large for gestational age and born to obese mothers (58,159-162). In a Canadian cohort of children exposed to GDM, 7% had IGT at age 7 to 11 years (162). In the Pima Indian population, as many as 70% of offspring exposed to diabetes in utero had type 2 diabetes at age 25 to 35 years (163). Breastfeeding may lower the risk (82,138,164). The importance of tight glycemic control during pregnancy to prevent these outcomes is not clearly established. The need for increased surveillance of these children requires further study.

Planning subsequent pregnancies

Women with previous GDM should plan future pregnancies in consultation with their healthcare providers (165,166). Glucose tolerance should be assessed prior to conception to assure normoglycemia at the time of conception, and any glucose abnormality should be treated. In an effort to reduce the risk of congenital anomalies and optimize pregnancy outcomes, all women should take a folic acid supplement of 0.4 to 1.0 mg (48).

OTHER RELEVANT GUIDELINES

Screening for Type 1 and Type 2 Diabetes, p. S14

Targets for Glycemic Control, p. S29

Chronic Kidney Disease in Diabetes, p. S126

Type 1 Diabetes in Children and Adolescents, p. S150

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Diabetes in the Elderly

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes in the elderly is metabolically distinct from and the approach to therapy should be different than in people <60 years of age.
- Sulfonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age.
- In elderly people, the use of premixed insulins as an alternative to mixing insulins minimizes dose errors.

INTRODUCTION

The definition of “elderly” varies, with some studies defining the elderly population as ≥ 60 years of age. Administrative guidelines frequently classify people > 65 years of age as elderly. Although there is no uniformly agreed-upon definition of elderly, it is generally accepted that this is a concept that reflects an age continuum starting sometime after age 60 and is characterized by a slow, progressive frailty that continues until the end of life (1).

PREVENTION OF DIABETES

Lifestyle interventions are effective in the prevention of diabetes in elderly people at high risk for the development of the disease (2,3). Acarbose (4) and rosiglitazone (5) are also effective in the prevention of diabetes in elderly people at high risk, but metformin is not (3).

MANAGEMENT

Glycemic control

As interdisciplinary interventions have been shown to improve glycemic control in elderly individuals with diabetes, these people should be referred to a diabetes healthcare team (6,7). The same glycemic targets apply to otherwise healthy elderly as to younger people with diabetes (8-18). In people with multiple comorbidities, a high level of functional dependency and limited life expectancy, the goal should be less stringent, and clinicians should try to avoid symptoms of hyperglycemia and prevent hypoglycemia.

Nutrition and physical activity

Nutrition education programs can improve metabolic control in ambulatory older people with diabetes (19). Physical training programs can be successfully implemented in older peo-

ple with diabetes, although comorbid conditions may prevent aerobic physical training in many patients, and increased activity levels may be difficult to sustain. While the effects of aerobic exercise programs on glucose and lipid metabolism are inconsistent (20-23), resistance training has been shown to result in modest improvements in glycemic control, as well as improvements in strength, body composition and mobility (24-28). However, it appears difficult to maintain these changes outside of a supervised setting (29).

Oral antihyperglycemic agents

In lean elderly people with type 2 diabetes, the principal metabolic defect is impairment in glucose-induced insulin secretion (30). Therefore, initial therapy for these individuals should involve agents that stimulate insulin secretion. In obese elderly people with type 2 diabetes, the principal metabolic defect is resistance to insulin-mediated glucose disposal, with insulin secretion being relatively preserved (31-33). Initial therapy for obese older people with diabetes should involve agents that improve insulin resistance.

Alpha-glucosidase inhibitors are modestly effective in older people with diabetes, but a substantial percentage of individuals cannot tolerate them because of gastrointestinal side effects (34-38).

Thiazolidinediones are effective agents, but are associated with an increased incidence of edema and congestive heart failure (CHF) in older people and should be used with caution in individuals with cardiovascular disease (CVD) (39-43). When used as monotherapy, they are less likely to fail than metformin or glyburide (43).

Sulfonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age (44) and appears to be higher with glyburide (45,46). Gliclazide and glimepiride are preferred over glyburide in the elderly because they are associated with a lower frequency of hypoglycemic and CV events (47-49). A long-acting formulation of gliclazide resulted in equivalent glycemic control and the same frequency of hypoglycemic events as regular gliclazide in the elderly (50), and appears to result in a lower frequency of hypoglycemic events than glimepiride (51).

Meglitinides (repaglinide and nateglinide) are associated with a lower frequency of hypoglycemia in the elderly compared to glyburide (52,53), and would be preferred in individuals with irregular eating habits.

Insulin therapy

Insulin regimens in the elderly should be individualized and selected to promote patient safety. In elderly people, the use of premixed insulins as an alternative to mixing insulins (54) and prefilled insulin pens as an alternative to conventional syringes (55,56) minimizes dose errors and may improve glycemic control. Rapid-acting insulin analogue mixtures can be used and be administered after meals (57-59), although recent data suggest that the kinetics of regular and rapid-acting insulin are similar in the elderly (60). Multiple daily injections (MDI) may be associated with greater improvements in glycemic control, health status and mood than twice-daily injections of long-acting insulin (61). In older people with poorly controlled type 2 diabetes requiring insulin, both continuous subcutaneous insulin infusion (CSII) and MDI can result in excellent glycemic control, with good safety and patient satisfaction (62). One study demonstrated equivalent glycemic control in older people treated with either twice-daily insulin injections or a combination of a single injection of NPH insulin with an oral antihyperglycemic agent (63). Another study demonstrated that once-daily glargine with continuation of an oral antihyperglycemic agent resulted in better glycemic control and a reduced rate of hypoglycemia when compared to twice-daily injections of 30/70 insulin (64).

Prevention and treatment of complications

Hypertension

Treatment of isolated systolic hypertension or combined systolic and diastolic hypertension in elderly people with diabetes is associated with a significant reduction in CV morbidity and mortality (65-68). Treatment of isolated systolic hypertension may also preserve renal function in elderly people with diabetes (69).

Several different classes of antihypertensive agents have been shown to be effective in reducing the risk of CV events and end-stage renal disease, including thiazide-like diuretics, long-acting calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (65-75). Any of these agents is a reasonable first choice (70-72), although the calcium channel blocker amlodipine may be associated with an increased risk of CHF (72). Cardioselective beta blockers and alpha-adrenergic blockers are less likely to reduce CV risk than the above agents (70-74). ACE inhibitors may be particularly valuable for people with diabetes and ≥ 1 other CV risk factor (76,77).

Recent data suggest there has been a significant improvement in the last decade in the number of older people treated for hypertension, and therapies being used are more consistent with current clinical practice guidelines (78).

Dyslipidemia

The treatment of hypercholesterolemia with statins for both primary and secondary prevention of CV events has been shown in most, although not all, studies to significantly

reduce CV morbidity and mortality in older people with diabetes (79-88). The data on the use of fibrates in this patient population are equivocal (89,90).

Erectile dysfunction

Type 5 phosphodiesterase inhibitors appear to be effective for the treatment of erectile dysfunction in carefully selected elderly people with diabetes (91-93).

DIABETES IN NURSING HOMES

Diabetes is often undiagnosed in nursing home patients (94-96), and individuals frequently have established macro- and microvascular complications (97,98). In observational studies, the degree of glycemic control varies between different centres (94,98). Undernutrition is a major problem in people with diabetes living in nursing homes (98).

There are very few intervention studies on diabetes in nursing homes. The short-term substitution of a regular diet

RECOMMENDATIONS

1. In elderly individuals with impaired glucose tolerance, a structured program of lifestyle modification that includes moderate weight loss and regular physical activity should be considered to reduce the risk of type 2 diabetes [Grade A, Level 1A (2)].
2. Otherwise healthy elderly people with diabetes should be treated to achieve the same glycemic, blood pressure and lipid targets as younger people with diabetes [Grade D, Consensus]. In people with multiple comorbidities, a high level of functional dependency or limited life expectancy, the goals should be less stringent [Grade D, Consensus].
3. Elderly people with diabetes living in the community should be referred for interdisciplinary interventions involving education and support [Grade C, Level 3 (6,7,19)].
4. Aerobic exercise and/or resistance training may benefit elderly people with type 2 diabetes and should be recommended for those individuals in whom it is not contraindicated [Grade B, Level 2 (20,23-25)].
5. In elderly people with type 2 diabetes, sulfonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age [Grade D, Level 4 (44)]. In general, initial doses of sulfonylureas in the elderly should be half those used for younger people, and doses should be increased more slowly [Grade D, Consensus]. Gliclazide and gliclazide MR [Grade B, Level 2 (48,51)] and glimepiride [Grade C, Level 3 (49)] are the preferred sulfonylureas, as they are associated with a reduced frequency of hypoglycemic events. Meglitinides (repaglinide and nateglinide) should be considered in patients with irregular eating habits [Grade D, Consensus].
6. In elderly people, the use of premixed insulins and prefilled insulin pens as alternatives to mixing insulins should be considered to reduce dose errors, and to potentially improve glycemic control [Grade B, Level 2 (54-56)].

or a standard nutritional formula for a “diabetic diet” or a diabetic nutritional formula did not modify the level of glycemic control (99-101). For selected nursing home residents with type 2 diabetes, substitution of regular insulin by multiple injections with lispro insulin may improve glycemic control and glycosylated hemoglobin (A1C) levels with a reduced number of hypoglycemic episodes (102).

Screening for diabetes may be warranted in selected individuals. In the absence of positive intervention studies on morbidity or mortality in this population, the decision about screening for diabetes should be made on an individual basis.

OTHER RELEVANT GUIDELINES

Screening for Type 1 and Type 2 Diabetes, p. S14

Prevention of Diabetes, p. S17

Organization of Diabetes Care, p. S20

Self-management Education, p. S25

Targets for Glycemic Control, p. S29

Insulin Therapy in Type 1 Diabetes, p. S46

Pharmacologic Management of Type 2 Diabetes, p. S53

Hypoglycemia, p. S62

Screening for the Presence of Coronary Artery Disease, p. S99

Dyslipidemia, p. S107

Treatment of Hypertension, p. S115

Erectile Dysfunction, p. S147

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Type 2 Diabetes in Aboriginal Peoples

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Efforts to prevent diabetes should focus on all diabetes risk factors, including pregravid obesity, to reduce gestational diabetes mellitus, macrosomia and diabetes risk in offspring; promotion of breast-feeding; and prevention of childhood, adolescent and adult obesity.
- Routine medical care in Aboriginal peoples should include identification of modifiable risk factors (e.g. lack of physical activity, unhealthy eating habits, obesity resulting in elevated waist circumference and/or body mass index) in order to identify higher-risk individuals who would benefit from diabetes prevention strategies and counselling.
- Screening for diabetes in adults should be considered every 1 to 2 years in Aboriginal individuals with ≥ 1 additional risk factor(s). Screening every 2 years should also be considered from age 10 or established puberty in Aboriginal children with ≥ 1 additional risk factor(s).
- Treatment of diabetes in Aboriginal peoples should follow current clinical practice guidelines using Aboriginal-specific community diabetes management programs developed and delivered in partnership with the target communities.

INTRODUCTION

Canadian Aboriginal peoples are a heterogeneous population comprised of individuals of First Nations, Inuit and Métis heritage living in a range of environments from large cities to small, isolated communities. As in other countries, type 2 diabetes has reached epidemic proportions among Aboriginal peoples in Canada, with the national age-adjusted prevalence 3 to 5 times higher than that of the general population (1) and as high as 26% in individual communities (2). Aboriginal peoples are diagnosed with type 2 diabetes at a much younger age (1), with high rates of diabetes in children and adolescents (3). As well, Aboriginal women are at more than twice the risk of gestational diabetes mellitus (GDM) compared to non-Aboriginal women (4) and have high rates of pre-existing type 2 diabetes in pregnancy (5). Prediabetes and metabolic syndrome are also more common in these populations (6).

The high rate of type 2 diabetes is associated with increased rates of cardiovascular disease (CVD), peripheral arterial disease, neuropathy and renal disease in this popula-

tion (7). In Manitoba, it is estimated that between the years 1996 and 2016, there will be a 10-fold increase in CVD, a 10-fold increase in lower-extremity amputations, a 10-fold increase in dialysis starts and a 5-fold increase in blindness among Aboriginal peoples (8).

High rates of diabetes are likely the result of the interaction of genetic susceptibility and local genetic mutations with numerous social stressors and lifestyle factors (9-11). Decreased rates of physical activity and the replacement of traditional foods with highly refined foods have resulted in high rates of obesity and diabetes risk factors in children (12) and adults (13).

Indicators of insulin resistance and hyperinsulinemia (e.g. elevated body mass index [BMI] and waist circumference [WC], and metabolic syndrome) are strong predictors of risk for developing type 2 diabetes in Aboriginal peoples (14-16). Other predisposing factors include positive family history and maternal pregnancy complicated by frank diabetes or GDM (which lead to increased incidence of diabetes in the offspring) (17,18). As well, pregravid maternal obesity in Aboriginal populations is associated with increased risk of GDM and infant macrosomia (5). Rates of macrosomia continue to rise in northern communities (19), and infant macrosomia has been associated with increased rates of childhood obesity (20), and hence adolescent and adult obesity.

SCREENING

Due to the high prevalence of risk factors for diabetes in specific Aboriginal groups (6,12,13,20), routine medical care in Aboriginal peoples of all ages (starting in early childhood) should include identification of these modifiable risk factors (e.g. obesity, elevated WC or BMI, lack of physical activity, unhealthy eating habits), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to identify higher-risk individuals who would benefit from diabetes prevention strategies and individualized counselling. While WC is a more reliable predictor than BMI for development of diabetes (14), the standard cut-offs for BMI and WC should be used in Aboriginal populations.

As part of routine medical care provided to Aboriginal people, screening for diabetes with a fasting plasma glucose test should be considered every 1 to 2 years in individuals with ≥ 1 additional risk factor(s). Screening every 2 years should also be considered from age 10 or established puberty

(21) in Aboriginal children with ≥ 1 additional risk factor(s) (e.g. obesity, family history of type 2 diabetes, exposure to diabetes in utero, acanthosis nigricans, polycystic ovary syndrome [PCOS], hypertension, dyslipidemia and use of antipsychotic medications/atypical neuroleptics). An oral glucose tolerance test (OGTT) should be done annually in children who are very obese (BMI ≥ 99.5 percentile) (see "Type 2 Diabetes in Children and Adolescents," p. S162).

Those individuals with normal results but with diabetes risk factors (in addition to Aboriginal heritage) should receive post-test counselling on promotion of healthy lifestyles for diabetes prevention. Annual OGTT testing in individuals with prediabetes (IFG and/or IGT) or PCOS should be encouraged, as 20 to 50% of high-risk individuals with IFG may have a 2-hour plasma glucose ≥ 11.1 mmol/L (22).

PRIMARY PREVENTION

Efforts to prevent diabetes should focus on all diabetes risk factors, including pregravid obesity to reduce GDM, macrosomia and diabetes risk in offspring; promotion of breastfeeding; and prevention of childhood, adolescent and adult obesity.

Primary prevention of diabetes requires collaboration between community leaders, healthcare professionals and funding agencies. Several initiatives with community-researcher partnerships are ongoing, and include programs to mobilize entire communities, promote environmental changes and prevent GDM (23-27). These partnerships share the common values of incorporating traditions and local culture to promote empowerment, increased physical activity, balanced eating and healthy body weights. Such programs reinforce to individuals and families that they have some control over their risk for diabetes. This can impact positively on the approach to self-care and to the philosophy around family or community activities, all of which affect family members who already have the disease or are at risk for diabetes. However, there remains a lack of published evidence that these interventions result in a reduction in the incidence of diabetes in the target communities (27).

Prevention of childhood obesity through moderate interventions starting in infancy has been shown to be effective (28). In Zuni First Nations children, an educational component targeting decreased consumption of sugared beverages, knowledge of diabetes risk factors and a youth-oriented fitness centre significantly decreased insulin resistance (29). These types of interventions aimed at decreasing childhood obesity, as well as efforts to promote breast-feeding in the first year of life (30), may help to reduce the risk for diabetes. As well, strategies aimed at the prevention of maternal obesity prior to first conception or subsequent pregnancy may be important tools to decrease the incidence of GDM and type 2 diabetes in pregnancy, thereby potentially decreasing the incidence of diabetes in subsequent generations of Aboriginal Canadians (5,18,26).

MANAGEMENT

Treatment of diabetes in Aboriginal peoples should follow current clinical practice guidelines, with Aboriginal-specific community diabetes management programs developed and delivered in partnership with the target communities, reflecting a population health approach. Ideally, multidisciplinary teams should include community members with local knowledge and expertise. Diabetes education programs should consider various learning styles, incorporate local traditions and culture, promote traditional activities and foods (provided they are safe, acceptable and accessible) and, ideally, be taught in the language of the individual.

In Aboriginal communities, much of the responsibility for diabetes care falls to community health representatives (local lay healthcare providers), who are often already overburdened. These individuals are able to provide better care when they have appropriate additional training and can focus on diabetes. A number of communities have provided comprehensive diabetes training to local lay people, who can then combine their knowledge of diabetes with sensitivity to the culture and issues in their community.

Weight loss associated with a temporary return to a traditional hunter-gatherer lifestyle was shown to significantly improve glycemic control among adult male volunteers in an Australian Aboriginal community (31). A number of recent American studies have demonstrated that carbohydrate-restricted diets, which resemble traditional Aboriginal diets, have a salutary effect on diabetes and metabolic syndrome (32-37). A focus on dietary change to a more carbohydrate-restricted diet may be warranted in both the prevention and treatment of diabetes in Aboriginal populations.

Comprehensive management of diabetes in small remote communities remains difficult, due to discontinuities in staffing, lack of work-practice support and individuals' acceptance of services (38). In some communities, mobile teams of nurses, technicians and in some cases physicians assess and treat community members with diagnosed diabetes (39). Use of a nurse-directed hypertension treatment protocol has been shown to be effective in Aboriginal peoples in Northern Canada (40). Use of a nurse case manager in large urban centres (caring for a mean of 365 Aboriginal patients) was shown to be somewhat more effective than usual care when assessing diabetes care on multiple parameters, and may be an effective strategy for remote and poorly serviced communities (41). Retinal photography has been shown to be another effective strategy for screening for diabetic retinopathy in remote communities (42). Due to the heterogeneous settings of different high-risk groups, each community or region must determine the most cost-effective strategy to provide comprehensive diabetes care to best suit their reality.

In the United States, federally funded on-reserve programs include diabetes registries, use of flow charts, annual chart audits with continuous quality assurance, full-time

dedicated diabetes clinical staff (e.g. nurses) and funding for community initiatives. These programs have conclusively demonstrated improvements in conventional diabetes measures (e.g. decreased glycosylated hemoglobin, improved lipid profiles, reductions in blood pressure) (43). A similar national program should be established in Canada for on- and off-reserve Aboriginal communities.

RECOMMENDATIONS

1. Starting in early childhood, Aboriginal people should be routinely assessed for modifiable risk factors of diabetes (e.g. obesity, elevated WC, lack of physical activity, unhealthy eating habits), IFG or IGT in order to identify higher-risk individuals who would benefit from diabetes prevention strategies [Grade D, Consensus].
2. Screening for diabetes in Aboriginal children and adults should follow guidelines for high-risk populations (i.e. earlier and at more frequent intervals depending on presence of additional risk factors) [Grade D, Consensus].
3. Culturally appropriate primary prevention programs for children and adults should be initiated in and by Aboriginal communities to increase awareness of diabetes, increase physical activity, improve eating habits and achieve healthy body weights, and to promote an environment supportive of a healthy lifestyle [Grade D, Consensus].
4. Management of prediabetes and diabetes in Aboriginal people should follow the same clinical practice guidelines as those for the general population with recognition of, respect for and sensitivity to the unique language, cultural and geographic issues as they relate to diabetes care and education in Aboriginal communities across Canada [Grade D, Consensus].
5. Aboriginal peoples in Canada should have access in their communities to a diabetes management program that would include the hiring of diabetes healthcare professionals, the establishment of diabetes registries, and ongoing quality assurance programs [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Screening for Type 1 and Type 2 Diabetes, p. S14

Prevention of Diabetes, p. S17

Management of Obesity in Diabetes, p. S77

Type 2 Diabetes in Children and Adolescents, p. S162

RELATED WEBSITES

Aboriginal Diabetes Initiative, First Nations and Inuit Health Branch. Available at: <http://www.hc-sc.gc.ca/fnihb/cp/adi/index.htm>. Accessed September 1, 2008.

National Aboriginal Diabetes Association. Available at: <http://www.nada.ca>. Accessed September 1, 2008.

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Type 2 Diabetes in High-risk Ethnic Populations

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- There is some evidence to support the use of ethnic-specific body mass index and waist circumference cutoffs to improve risk stratification and targeted risk management.
- The complex interplay between cultural context and lifestyle supports the use of ethnic-specific community-based diabetes prevention programs that focus on lifestyle modification.
- High-risk ethnic patients develop diabetes complications, particularly cardiovascular disease and renal failure, much earlier than other populations, warranting aggressive management of relevant risk factors, including hypertension and dyslipidemia.

INTRODUCTION

The increase in immigration to Canada over the last 50 years has created a very ethnically diverse population. The 2006 census enumerated over 6 million foreign-born people in Canada, accounting for 19.8% of the total population, the highest proportion in 75 years (1). Among the foreign-born population who reported a mother tongue other than French or English, most reported Chinese languages (18.6%), followed by Italian (6.6%), Punjabi (5.9%), Spanish (5.8%), German (5.4%), Tagalog (4.8%) and Arabic (4.7%). Recent immigrants born in Asia (including the Middle East) comprise the largest proportion (58.3%) of newcomers to Canada, compared to 12.1% in 1971 (1). Toronto, Montreal and Vancouver are home to 68.9% of recent immigrants. In contrast, only 27.1% of Canada's total population lives in these 3 cities (1).

Ethnic disparities in diabetes prevalence have been well documented in the United Kingdom and the United States where, compared with the general population, individuals of South Asian, Chinese, African and Latin ancestry have higher rates of metabolic syndrome, impaired glucose tolerance (IGT), abdominal (central) obesity, insulin resistance (2-7), type 2 diabetes in childhood (8-10), gestational diabetes mellitus (11), and diagnosed and undiagnosed type 2 diabetes with onset at a younger age (12). Those with type 2 diabetes have poorer metabolic control (13-15) and experience higher rates of microvascular and macrovascular complications, which occur at younger ages than the general population (1,16-19). Individuals of South Asian descent represent Canada's fastest-growing immigrant population. Of all expa-

triate ethnic groups, they have the highest rates of morbidity and mortality from diabetes-related cardiovascular disease (CVD), with 40% higher age-standardized mortality from coronary artery disease than Caucasians (6,19-21).

Factors responsible for ethnic disparities in diabetes prevalence are multifactorial and include genetic susceptibility, insulin resistance, inadequate socioeconomic resources, self-care capacity challenges, degree of acculturation, health literacy, psychosocial stressors, differences in treatment response, and barriers to accessing healthcare. Traditional diabetes care systems designed for mainstream populations are often of limited relevance to culturally diverse populations, as these systems emphasize the reduction of behavioural risk factors and benefits of self-care behaviours, but ignore the social, cultural, economic and physical environments in which lifestyle practices are shaped and often constrained. There is growing evidence that diabetes prevention and management strategies that target the social determinants of health, offer group support, provide services of a multidisciplinary team that includes community members with local knowledge and expertise are designed with an affinity to the cultural traditions and socioeconomic realities of the target ethnic group, and are delivered in the language of the individual, are associated with improved clinical outcomes and reduced ethnic disparities (22-30).

SCREENING

As the relationship between body fat, waist circumference (WC) and disease varies between ethnic groups, there is some evidence to support the use of ethnic-specific body mass index (BMI) (31) and WC (32) cutoffs to improve risk stratification and targeted risk management in different ethnic groups. Asian-specific cutoffs for risk are BMI=22 to 25 kg/m² ("at risk"); and BMI ≥26 kg/m² ("at higher risk") (31), and WC ≥80 cm for women or ≥90 cm for men (32).

Opportunistic screening by family physicians is ideal but not always accessible to high-risk new immigrant groups. Targeted, ethnic-specific, stepped screening approaches offered in the community, and developed and delivered in partnership with the target communities may refine risk stratification and identification of those who would benefit most from a visit to a family physician (5).

In patients in whom a suspicion of prediabetes is high, a 2-hour 75-g oral glucose tolerance test may be considered.

PRIMARY PREVENTION

Several large primary prevention clinical trials published in the past 5 years have shown that progression of IGT can be prevented or delayed with lifestyle or pharmacological interventions. In the Da Qing study (with 577 Chinese subjects with IGT) and a Japanese study (with 458 Japanese subjects with IGT), lifestyle interventions were associated with 46 and 67% reductions, respectively, in the incidence of type 2 diabetes (33,34). The Diabetes Prevention Program, a large prospective randomized clinical trial in 3234 American adults with impaired fasting glucose (IFG) or IGT, demonstrated that lifestyle modifications reduced the incidence of type 2 diabetes in a variety of high-risk racial/ethnic groups (35). The recently published Indian Diabetes Prevention Program demonstrated a relative risk reduction of 28.5% with lifestyle intervention in native Asian Indians with IGT who were younger, leaner and more insulin resistant than the above populations (36). Progression of IGT to diabetes was 18.3% per year. In a 3-year follow-up, 55% of the nonobese yet highly insulin-resistant Indian population with IGT developed diabetes (23).

The complex interplay between cultural context and lifestyle supports the use of ethnic-specific, community diabetes prevention programs that focus on lifestyle modification. They should be developed and delivered in partnership with the target communities (5).

MANAGEMENT

The cultural dynamics influencing chronic illness management are complex and deeply rooted in the cultural traditions and fabric of ethnic communities. There is a growing body of evidence supporting the use of ethnic-specific community diabetes management programs that reflect the unique socio-cultural dynamics of and are delivered in partnership with the target communities (5,24-26). Individuals from high-risk ethnic populations develop diabetes complications, particularly CVD and renal failure, much earlier than other populations. Given the high CV mortality in South Asians, aggressive management of risk factors, including hypertension and dyslipidemia, is warranted to reduce morbidity and mortality (6).

RECOMMENDATIONS

1. High-risk ethnic peoples should be screened for diabetes according to clinical practice guidelines [Grade D, Consensus]. Ethnic-specific BMI and WC cutoff points should be used for risk stratification [Grade D, Consensus]. Where access to screening by a family physician is not available, targeted community screening programs should be provided for those at high risk of diabetes [Grade D, Consensus].
2. Community-based prevention and management programs aimed at high-risk ethnic peoples should be developed and delivered in partnership with target communities, and should reflect the local ethnocultural representation [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

- Screening for Type 1 and Type 2 Diabetes, p. S14
- Prevention of Diabetes, p. S17
- Organization of Diabetes Care, p. S20
- Self-management Education, p. S25
- Identification of Individuals at High Risk of Coronary Events p. S95
- Type 2 Diabetes in Children and Adolescents, p. S162

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Appendix 1

*Etiologic Classification of Diabetes Mellitus**

Type 1 diabetes mellitus Beta cell destruction, usually leading to absolute insulin deficiency <ul style="list-style-type: none"> • Immune-mediated • Idiopathic 	
Type 2 diabetes mellitus May range from predominant insulin resistance with relative insulin deficiency to predominant secretory defect with insulin resistance	
Gestational diabetes mellitus Onset or first recognition of glucose intolerance during pregnancy	
Other specific types	
Genetic defects of beta cell function <ul style="list-style-type: none"> • Chromosome 20, HNF-4alpha (formerly MODY1) • Chromosome 7, glucokinase (formerly MODY2) • Chromosome 12, HNF-1alpha (formerly MODY3) • Chromosome 13, IPF-1 (formerly MODY4) • Chromosome 17, HNF-1beta (MODY5) • Chromosome 2, <i>NeuroD1</i> (MODY6) • Mitochondrial DNA • Neonatal diabetes (e.g. due to Kir6.2 mutation) • Others Genetic defects in insulin action <ul style="list-style-type: none"> • Leprechaunism • Lipomatrophic diabetes • Rabson-Mendenhall syndrome • Type A insulin resistance • Others Diseases of the pancreas <ul style="list-style-type: none"> • Cystic fibrosis • Fibrocalculous pancreatopathy • Hemochromatosis • Neoplasia • Pancreatitis • Trauma/pancreatectomy • Others Endocrinopathies <ul style="list-style-type: none"> • Acromegaly • Aldosteronoma • Cushing syndrome • Glucagonoma • Hyperthyroidism • Pheochromocytoma • Somatostatinoma • Others 	Infections <ul style="list-style-type: none"> • Congenital rubella • Cytomegalovirus • Others Uncommon forms of immune-mediated diabetes <ul style="list-style-type: none"> • Anti-insulin receptor antibodies • "Stiff-man" syndrome • Others Drug- or chemical-induced <ul style="list-style-type: none"> • Atypical antipsychotics • Beta-adrenergic agonists • Cyclosporine • Diazoxide • Glucocorticoids • Interferon alfa • Nicotinic acid • Pentamidine • Phenytoin • Protease inhibitors • Thiazide diuretics • Thyroid hormone • Others Other genetic syndromes sometimes associated with diabetes <ul style="list-style-type: none"> • Down syndrome • Friedreich ataxia • Huntington chorea • Klinefelter syndrome • Laurence-Moon-Bardet-Biedl syndrome • Myotonic dystrophy • Porphyria • Prader-Willi syndrome • Turner syndrome • Wolfram syndrome • Others

*Patients with any form of diabetes may require insulin treatment at some stage of their illness. Such use of insulin does not, of itself, classify the patient

HNF = hepatocyte nuclear factor

IPF = insulin promoter factor

MODY = maturity-onset diabetes of the young

Adapted with permission from: American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2007;30(suppl 1):S42-S47.

Care	Objective	Target
Self-monitoring of blood glucose	<ul style="list-style-type: none"> Reinforce patient's responsibility for regular monitoring as appropriate Ensure patient can use glucose meter; interpret SMBG results and modify treatment as needed Develop an SMBG schedule with patient and review records 	Preprandial (mmol/L) 4.0–7.0 for most patients 2-hour postprandial (mmol/L) 5.0–10.0 for most patients 5.0–8.0 if not achieving A1C target
Blood glucose control	<ul style="list-style-type: none"> Measure A1C every 3 months for most adults Consider testing at least every 6 months in adults during periods of treatment and lifestyle stability, and when glycemic targets are being consistently achieved 	A1C ≤7.0% for most patients See "Targets," p. S29
Blood glucose meter accuracy	<ul style="list-style-type: none"> Compare meter results with laboratory measurements at least annually, and when indicators of glycemic control do not match meter 	Simultaneous fasting glucose/meter lab comparison within 20%
Hypertension	<ul style="list-style-type: none"> Measure BP at diagnosis of diabetes and at every diabetes clinic visit 	<130/80 mm Hg
Waist circumference	<ul style="list-style-type: none"> Measure as an indicator of abdominal fat 	Target WC: M <102 cm, F <88 cm (see ethnic-specific values in "Management of Obesity in Diabetes," p. S77)
Body mass index	<ul style="list-style-type: none"> Calculate BMI: mass in kg/(height in m)² 	Target BMI: 18.5–24.9 kg/m²
Nutrition	<ul style="list-style-type: none"> Encourage nutrition therapy (by a Registered Dietitian) as an integral part of treatment and self-management (can reduce A1C by 1–2%) 	Meet nutritional needs by following <i>Eating Well with Canada's Food Guide</i>
Physical activity	<ul style="list-style-type: none"> Discuss and encourage aerobic and resistance exercise Consider exercise ECG stress test for previously sedentary individuals at high risk for CAD planning exercise more vigorous than brisk walking 	Aerobic: ≥150 minutes/week Resistance: 3 sessions/week
Smoking	<ul style="list-style-type: none"> Encourage patient to stop at each visit; provide support as needed 	Smoking cessation
Retinopathy	<ul style="list-style-type: none"> Type 1 diabetes: Screen 5 years after diagnosis, then rescreen annually Type 2 diabetes: Screen at diagnosis, then every 1–2 years if no retinopathy present Screening should be conducted by an experienced eye care professional 	Early detection and treatment
Chronic kidney disease	<ul style="list-style-type: none"> Identification of CKD requires screening for proteinuria using random urine ACR and assessment of renal function using a serum creatinine converted to eGFR Type 1 diabetes: In adults, screen after 5 years duration of diabetes, then annually if no CKD Type 2 diabetes: Screen at diagnosis, then annually if no CKD If CKD present, perform ACR and eGFR at least every 6 months 	ACR (mg/mmol) Normal: M <2.0; F <2.8 Microalbuminuria: M 2.0–20.0, F 2.8–28.0 Macroalbuminuria: M >20.0, F >28.0 CKD if eGFR ≤60 mL/min
Neuropathy/foot examination	<ul style="list-style-type: none"> Type 1 diabetes: Screen 5 years after diagnosis, then rescreen annually Type 2 diabetes: Screen at diagnosis, then annually Screen for neuropathy with 10-g monofilament or 128-Hz tuning fork at dorsum of great toe. In foot exam, look for structural abnormalities, neuropathy, arterial disease, ulceration, infection 	Early detection and treatment If neuropathy present: foot care education, specialized footwear, smoking cessation If ulcer present: manage by multidisciplinary team with expertise
CAD assessment	<ul style="list-style-type: none"> Conduct CAD risk assessment periodically: CV history, lifestyle, duration of diabetes, sexual function, abdominal obesity, lipid profile, BP, reduced pulses, bruits, glycemic control, retinopathy, eGFR, ACR Measure baseline resting ECG, then every 2 years if: age >40 years, duration of diabetes >15 years, symptoms, hypertension, proteinuria, bruits or reduced pulses High-risk categories include: <ul style="list-style-type: none"> Men ≥45 years, women ≥50 years or Men <45 years, women <50 years with ≥1 of macrovascular disease, microvascular disease (especially retinopathy, nephropathy), multiple additional risk factors (especially family history of premature coronary or cerebrovascular disease in 1st-degree relative), extreme single risk (e.g. LDL-C >5.0 mmol/L, systolic BP >180 mm Hg) or duration of diabetes >15 years and age >30 years 	Vascular protection: first priority in prevention of diabetes complications is reduction of CV risk by vascular protection through a comprehensive multifaceted approach: <ul style="list-style-type: none"> All people with diabetes: optimize BP, glycemic control and lifestyle (weight, exercise, smoking) People with diabetes and at high risk of CV event, additional interventions: ACE inhibitor/ARB antiplatelet therapy (as indicated) and lipid-lowering medication (primarily statins)
Dyslipidemia	<ul style="list-style-type: none"> Measure fasting lipid levels (TC, HDL-C, TG and calculated LDL-C) at diagnosis of diabetes, then every 1–3 years as clinically indicated. Test more frequently if treatment initiated 	Lipid targets for those at high risk for CAD: <ul style="list-style-type: none"> Primary target: LDL-C ≤2.0 mmol/L Secondary target: TC/HDL-C <4.0

Care objectives: People with diabetes will have better outcomes if primary healthcare providers: 1) identify patients with diabetes in their practice; 2) assist them by incorporating the suggested care objectives; 3) schedule diabetes-focused visits; and 4) use diabetes patient care flow sheets and systematic recall for visits.

Appendix 3

Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

All people starting insulin should be counselled about the recognition, prevention and treatment of hypoglycemia. Consider a change in type or timing of insulin administration if glycemic targets are not being reached.

Example A: Basal insulin (Humulin-N, Lantus, Levemir, Novolin ge NPH) added to oral antihyperglycemic agents

- Insulin should be titrated to achieve target fasting BG levels of 4.0 to 7.0 mmol/L.
- Individuals can be taught self-titration, or titration may be done in conjunction with a healthcare provider.
- Suggested starting dose is 10 units once daily at bedtime.
- Suggested titration is 1 unit per day until target is reached.
- A lower starting dose, slower titration and higher targets may be considered for elderly or normal-weight subjects.
- In order to safely titrate insulin, patients must perform SMBG at least once a day fasting.
- Insulin dose should not be increased if the individual experiences 2 episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- For BG levels consistently <5.5 mmol/L, a reduction of 1 to 2 units of insulin may be considered to avoid nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example B: Premixed insulin (Novolin 30/70, Humulin 30/70, NovoMix 30, Mix 25 or Mix 50) added to oral antihyperglycemic agents

- Suggested starting dose is 5 to 10 units once or twice daily (prebreakfast and/or presupper).
- Suggested titration is 1 to 2 units added to prebreakfast dose and/or presupper dose daily until target BG values are reached based on prebreakfast and presupper BG readings.
- Prebreakfast premixed insulin achieves presupper target BG value (4.0 to 7.0 mmol/L).
- Presupper premixed insulin achieves target fasting BG value (4.0 to 7.0 mmol/L).
- 30/70 premixed insulin should be given 30 to 45 minutes before meals.
- NovoMix 30 and Mix 25 premixed insulin should be given immediately before eating.
- Stop increasing insulin when both target BG levels are reached.
- If both BG targets are not reached, continue to increase the relevant dose until both targets achieved.
- The individual needs to self-monitor BG at least twice daily to safely titrate insulin.
- Insulin dose should not be increased if the individual experiences 2 or more episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example C: Intensive insulin therapy with basal/bolus insulin

- Calculate total daily dose of 0.3 to 0.5 units/kg then distribute as follows:
 - a. 40% of total insulin dose as basal insulin (Humulin-N, Lantus, Levemir, Novolin ge NPH).
 - b. 20% of total insulin as bolus (prandial) insulin (Apidra, Humalog, Humulin R, Novolin ge Toronto, NovoRapid) 3 times per day rapid-acting insulin analogue or short-acting insulin).

Sample Instructions for Patients With Type 2 Diabetes Who Are Starting and Adjusting Insulin

You will be taking insulin _____ at _____.

It is important that you continue to take your other diabetes medications as prescribed unless you have been told to change the dose or stop them.

How to adjust your insulin dose

- Your target fasting blood glucose level is _____ mmol/L.
- You will inject _____ units of _____ at _____.
- You will continue to increase your insulin dose by _____ unit(s) every _____ day(s) until your fasting blood glucose level is _____ mmol/L.
- Do not increase your insulin when your fasting blood glucose is _____ mmol/L.
- You should call for further instructions when your blood glucose reaches _____ mmol/L for 3 or more days: phone number _____.
- A side effect of insulin is low blood glucose (hypoglycemia); low blood glucose can occur with too much insulin, increased activity or not enough food.

Monitoring your blood glucose

- It is important to test your blood glucose while your insulin treatment is being modified.
- You should test your blood glucose and record the value every day before breakfast and _____.
- Test before each meal, unless you are instructed differently.
- It is important to record your blood glucose values and any changes in activity or food in your diary and bring this to your next appointment; this information helps us to understand your diabetes control.
- Unless otherwise instructed, you are trying to reach a target blood glucose of 4.0 to 7.0 mmol/L before meals, and 5.0 to 8.0 mmol/L after meals.
- If you think your blood glucose is low, check it and record that information in your diary.

Instructions for taking your diabetes medications

Current medications	Dose	Time of day	Special instructions

Appendix 4

Rapid Screening for Diabetic Neuropathy

Multiple screening methods are published. These methods (1) are designed to screen for the presence or absence of diabetic neuropathy, as opposed to screening for specific sites on the feet that are at risk of ulceration (multisite testing). If neuropathy is identified by either of these methods, other sites may be tested to identify high-risk areas for ulceration.

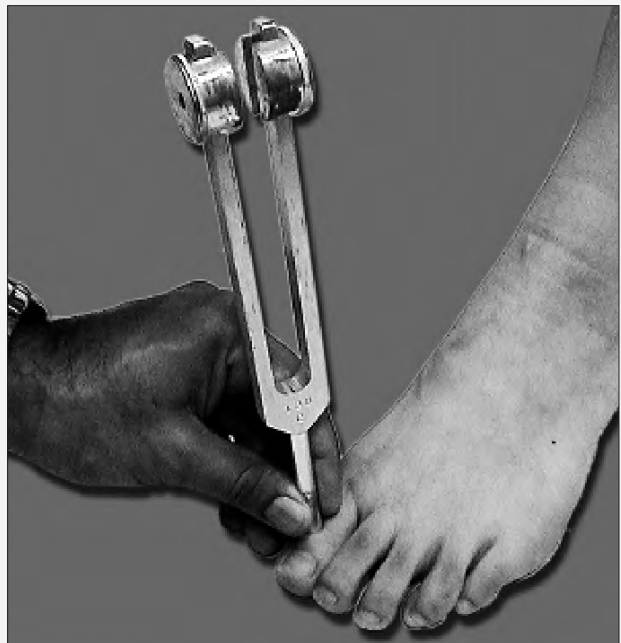
Rapid Screening for Diabetic Neuropathy Using the 10-g Semmes-Weinstein Monofilament

1. Show the 10-g Semmes-Weinstein monofilament to the patient.
2. Touch it first to the patient's forehead or sternum so that the sensation is understood.
3. Instruct the patient to say "yes" every time the monofilament stimulus is perceived.
4. With the patient's eyes closed, apply the monofilament to the dorsum of the great toe proximal to the nail bed as shown in the illustration below. Use a smooth motion – touch the skin, bend the filament for a full second, then lift from the skin.
5. Perform this stimulus 4 times per foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
6. Add up all correct stimuli for a score out of 8. A score of 7 or 8 correct responses likely rules out the presence of neuropathy.



Rapid Screening for Diabetic Neuropathy Using the 128-Hz Vibration Tuning Fork (The "On-Off" Method)

1. Strike the tuning fork against the palm of your hand hard enough that it will vibrate for approximately 40 seconds.
2. Apply the base of the tuning fork to the patient's forehead or sternum and ensure that the vibration sensation (not just the touch sensation) is understood.
3. With the patient's eyes closed, apply the tuning fork to the bony prominence situated at the dorsum of the first toe just proximal to the nail bed. Ask if the vibration sensation is perceived.
4. Ask the patient to tell you when the vibration stimulus is stopped, and then dampen the tuning fork with your other hand.
5. One point is assigned for each vibration sensation perceived (vibration "on"). Another point is assigned if the correct timing of dampening of the vibration is perceived (vibration "off").
6. Repeat this procedure again on the same foot, then twice on the other foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
7. Add up all correct stimuli for a score out of 8. A score of 7 or 8 correct responses likely rules out the presence of neuropathy.



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Appendix 5

Diabetes and Foot Care: A Patient's Checklist

Many people with diabetes have problems with their feet. Ask your doctor to explain your risk factors for foot problems. You can prevent serious foot problems by following these basic guidelines.

DO...	DON'T...
...check your feet every day for cuts, cracks, bruises, blisters, sores, infections or unusual markings.	...cut your own corns or calluses.
...use a mirror to see the bottom of your feet if you can't lift them up.	...treat your own in-growing toenails or slivers with a razor or scissors. See your doctor or foot care specialist.
...check the colour of your legs and feet. If there is swelling, warmth or redness or if you have pain, see your doctor or foot specialist right away.	...use over-the-counter medications to treat corns and warts. They are dangerous for people with diabetes.
... clean a cut or scratch with a mild soap and water and cover with a dry dressing for sensitive skin.	...apply heat to your feet with a hot water bottle or electric blanket. You could burn your feet without realizing it.
...trim your nails straight across.	...soak your feet.
...wash and dry your feet every day, especially between the toes.	...take very hot baths.
...apply a good skin lotion every day on your heels and soles. Wipe off any excess lotion.	...use lotion between your toes.
...change your socks every day.	...walk barefoot inside or outside.
...always wear a good supportive shoe.	...wear tight socks, garters or elastics, or knee highs.
...always wear professionally fitted shoes from a reputable store. Professionally fitted orthotics may help.	...wear over-the-counter insoles – they can cause blisters if they are not right for your feet.
...choose shoes with low heels (under 5 cm high).	...sit for long periods of time.
...buy shoes in the late afternoon (since your feet swell slightly by then).	...smoke.
...avoid extreme cold and heat (including the sun).	
...exercise regularly.	
...see a foot care specialist if you need advice or treatment.	

Adapted with permission from: Casella A. Feeling well...diabetes and foot care, a patient's checklist. *Knowing Diabetes*. © Diabetes Hamilton, 2002

Appendix 6

Diabetic Foot Ulcers: Essentials of Management

1. Assess underlying cause(s): neuropathy and/or ischemia.
2. Ulcers should be probed with a blunt-tipped instrument to detect sinus tracks or palpable bone suggestive of deep infections.
3. Plantar-surface ulcers require pressure relief. Individuals with plantar-surface foot ulcers should be non-weight-bearing as much as possible and utilize off-loading footwear or appliances (1).
4. Clinically noninfected ulcers do not routinely require cultures or antibiotics (2).
5. More serious infections in chronic foot ulcers tend to be polymicrobial and typically require empiric use of broad spectrum systemic antibiotics as soon as possible. Antibiotics can be subsequently tailored according to culture and sensitivity results. Cultures obtained by curettage or biopsy tend to be more reliable than surface swabs (3).
6. Wound bed preparation involves debridement of necrotic tissue (neuropathic wounds and noncritical ischemic wounds only) and maintenance of adequate moist wound environment with appropriate wound dressings. Hydrogels are used to increase wound bed moisture in dry or minimally draining neuropathic ulcers. Dressings that provide therapeutic levels of ionic silver or iodine may reduce critical degrees of wound bacterial colonization (4).
7. Comorbidities need to be managed (e.g. hyperglycemia).
8. Refer to a specialized wound clinic where available.

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