TYPE 2 DIABETES

A HEALTHCARE PROFESSIONAL'S **GUIDE TO TREATMENT**

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CONTENTS

Note to readers: The contents herein represent the opinions and clinical experience of the author. This booklet is not intended to be a comprehensive text on diabetes management, but rather a user-friendly guide to key management principles for use in the primary care setting. Healthcare professionals must consider the needs of their individual patients and use clinical judgment when applying the information in this document. Readers who may be interested in more detail and references are referred to the most recent Canadian Diabetes Association clinical practice guidelines, which are available at www.diabetes.ca. In addition, physicians should consult the most recent version of the *Compendium of Pharmaceuticals and Specialties* for complete prescribing information and product monographs.

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Diabetes in Canada

Type 2 diabetes is a serious chronic disease that is reaching epidemic proportions in Canada and around the world. It is associated with significant long-term complications, particularly damage, dysfunction and failure of the kidney, eye, nerves, heart and blood vessels. These complications impact negatively on quality of life and on healthcare costs.

Population-based studies suggest that the prevalence of diabetes in Canada may be higher than 7.0%.[1] It is estimated that approximately one-third of adults with diabetes are unaware that they have the disease.[2] A Canadian study assessed the prevalence of undiagnosed diabetes and glucose intolerance in individuals aged 40 and over who visited their family doctor for routine care.[3] About 16.4% had known diabetes, 2.2% had undiagnosed diabetes and 3.5% had glucose intolerance. Therefore, one in five such patients visiting their physician will have diabetes or prediabetes.

Age is an important risk factor for diabetes, as the incidence increases with age. It is estimated that the number of people with diabetes will double in the next 10 years, in large part due to the aging "baby boomer" population. The annual cost to the Canadian healthcare system is currently estimated at approximately $12 billion and if left unchecked, could climb to nearly $17 billion by 2020.[4] The incidence and related costs will continue to increase unless effective prevention strategies can be implemented.

In Canada, 95% of people with type 2 diabetes are treated by a primary care practitioner, whereas 80% of type 1 patients are followed by an endocrinologist or diabetes treatment centre.[5] Thus, as primary care providers, we need to develop the expertise to function as a key member of the multidisciplinary healthcare team for patients with type 2 diabetes. The DICE study, published in 2005, showed that in primary care in Canada, half of patients with type 2 diabetes do not reach CDA-recommended treatment targets. Furthermore, glycemic control erodes with duration of disease. These patients also have a high burden of comorbidities: hypertension 63%, dyslipidemia 59%, macrovascular complications 29%, and microvascular complications 39%.[6] Improving the quality of life for our patients with diabetes will require multifactorial[7] and more intensive management of diabetes.

We are challenged daily to provide the most appropriate treatment and care for our patients, often under time constraints and with limited tools.

This booklet is intended to serve as quick reference document on current approaches to screening, monitoring and treatment of diabetes and its related complications.

Development of Type 2 Diabetes

Decreasing secretory capacity of the beta cell is always present when glucose levels start to rise. Hyperglycemia is thus the result of the dual defects of insulin resistance and relative insulin deficit, complicated by glucoregulatory dysfunction, due to deficient secretion of the incretin hormone glucagon-like peptide-1 (GLP-1).

The following factors appear to be involved in the development of type 2 diabetes.

1. Diabetes begins with a genetic predisposition to beta cell deficiency in secretion and action of insulin, and to excess energy efficiency, which results from exposure to an excess of calories, both through increased intake (energy-dense foods) and reduced output (a sedentary lifestyle).

2. With the expansion of visceral fat stores comes an increase of hormones (e.g. resistin, fasting-induced adipose factor) and intermediate metabolites (free fatty acids), which interfere with insulin action.

3. Insulin resistance ensues, accompanied by hyperinsulinemia, which occurs as the demand for insulin grows. Insulin resistance and hyperinsulinemia are precursors for future diabetes. Most people affected by type 2 diabetes are insulin-resistant.

4. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) occur after insulin resistance and are considered to be prediabetic stages. These stages can occur for varying lengths of time in different individuals, depending on environmental factors and an individual's genetic makeup. Some people may progress rapidly to overt type 2 diabetes, while others

progress gradually. A small proportion may even recover from this intermediate stage: this recovery is called reversion to normal glucose tolerance.

5. Incretin deficiency. The incretin system is one of the mechanisms that the body has to regulate energy. Normally, when food passes from the stomach to the ileum, the cells of the ileum release the intestinal hormone GLP-1, which has multiple actions—to increase satiety, thereby decreasing oral intake; to slow gastric emptying; to decrease glucagon secretion from the alpha cells of the pancreas (which in turn decreases glucose formation by the liver); and to increase insulin production in a glucose-dependant manner.

DEFINITIONS, SCREENING AND DIAGNOSIS

Diabetes

Type 2 diabetes is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action (insulin resistance), or both. Insulin sensitivity is the ability of a certain amount of insulin to affect blood glucose levels. Insulin resistance is a decrease in insulin sensitivity. Risk factors for diabetes are listed in Table 1. Reduced physical activity and being overweight are the major precursors of, and the most modifiable risk factors for, diabetes. Screening and diagnostic information are presented in Tables 2, 3 and 4.

Table 1. Primary risk factors for type 2 diabetes [1]

- First-degree relative with diabetes
- Age 40 years and older
- Member of high-risk population (e.g. people of Aboriginal, Hispanic, Asian, South Asian or African descent)
- History of IGT or IFG
- Dyslipidemia
- Hypertension
- Overweight
- Abdominal obesity
- Vascular disease
- Presence of complications associated with diabetes
- History of gestational diabetes mellitus (GDM)
- History of delivery of a macrosomic infant
- Polycystic ovary syndrome
- Acanthosis nigricans
- Schizophrenia

Table 2. Screening for diabetes [1]

- Screening for type 2 diabetes using an FPG should be performed every 3 years in people ≥40 years of age.
- Screen earlier and/or more frequently in people with additional risk factors (see Table below).
- Testing with a 2hPG in a 75-g OGTT is indicated when the FPG is 6.1 to 6.9 mmol/L, and should be considered when the FPG of 5.6 to 6.0 mmol/L when suspicion of type 2 diabetes or IGT is high (i.e. in those individual with ≥1 risk factors).

Table 3. Diagnosis of diabetes [1]

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.

Table 4. Plasma glucose levels for diagnosing IFG, IGT, and diabetes [1]

	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

Prediabetes

For IFG or IGT, the term prediabetes is commonly used, as it identifies those individuals at high risk for development of diabetes and cardiovascular disease (CVD). Plasma glucose levels for diagnosing prediabetes are shown in Table 4. The vast majority of these people will also have the metabolic syndrome. The aim in treating prediabetes is to prevent conversion to diabetes, which has been shown to occur at an incident rate up to 11 per hundred person years-years of follow-up).[8]

Intensive lifestyle management, including exercise for 30 minutes per day and a weight loss of 5 to 7% of total body weight, can decrease new onset of diabetes by almost 60%.[8-11] In individuals with IGT, new-onset diabetes can be reduced by approximately 30% with metformin (Glucophage),[8] or acarbose (Glucobay).[12] Rosiglitazone (Avandia) and the combination of rosiglitazone and metformin (Avandamet) have been shown to be associated with an approximately 60%[13] and 66% reduction,[14] respectively, in conversion of prediabetes to diabetes.

Metabolic syndrome

A constellation of certain features–including central obesity, hypertension, dyslipidemia and dysglycemia–is known as the "metabolic syndrome." The metabolic syndrome is very common, affecting almost 45% of the US population over age 50.[15] It is estimated that approximately 87% of people with type 2 diabetes also have the metabolic syndrome.[15] The prevalence of coronary artery disease (CAD) increases significantly with the metabolic syndrome. Those with metabolic syndrome but without diabetes have a CAD prevalence of 14%. Individuals with the metabolic syndrome and diabetes have a CAD prevalence of 19%.[15] Those with metabolic syndrome are also at very high risk of developing type 2 diabetes. As well, the metabolic syndrome is associated with increased CVD risks that are almost identical to type 2 diabetes.[16] Table 5 provides the most recent harmonized definition of metabolic syndrome. [17]

As risk factors tend to be associated, patients with one feature of the metabolic syndrome should be screened for each of the other features. (See Screening, Monitoring & Management of Complications & Co-morbidities on p. 47). CV risks increase dramatically with the number of features of the metabolic syndrome; hence, aggressive management of all risk factors is necessary

to lower CV risk. Sustained lifestyle measures of increased and regular exercise and decreased weight are indicated for patients with metabolic syndrome. With abdominal obesity, even modest weight loss may significantly reduce visceral fat accumulation. Exercise, weight loss and smoking cessation may increase high-density lipoprotein cholesterol (HDL-C) and lower triglycerides (TG) and blood pressure (BP).

Table 5. Clinical identification of the metabolic syndrome [17]

Diagnostic criteria	When ≥3 risk determinants are present
BG	**FPG ≥5.6 mmol/L** (or receiving treatment for elevated glucose)
BP	**≥130/85 mm Hg** (or receiving treatment for previously diagnosed hypertension)
TG	**≥1.7 mmol/L** (or receiving treatment)
HDL-C	**<1.0 mmol/L (men)** **<1.3 mmol/L (women)** (or receiving treatment)
Abdominal obesity	**Europids / Sub-Saharan Africans / Eastern Mediterranean and Middle East (Arab) populations:** WC ≥94 cm (men) WC ≥80 cm (women)
	Asian (including Japanese) / Asian / Chinese / Japanese / Ethnic South and Central American populations: WC ≥90 cm (men) WC ≥80 cm (women)
	Canada / United States / European WC ≥102 cm (men) WC ≥88 cm (women)

DIABETES KNOWLEDGE CHECKLIST

Test your diabetes knowledge.

Did you know…?

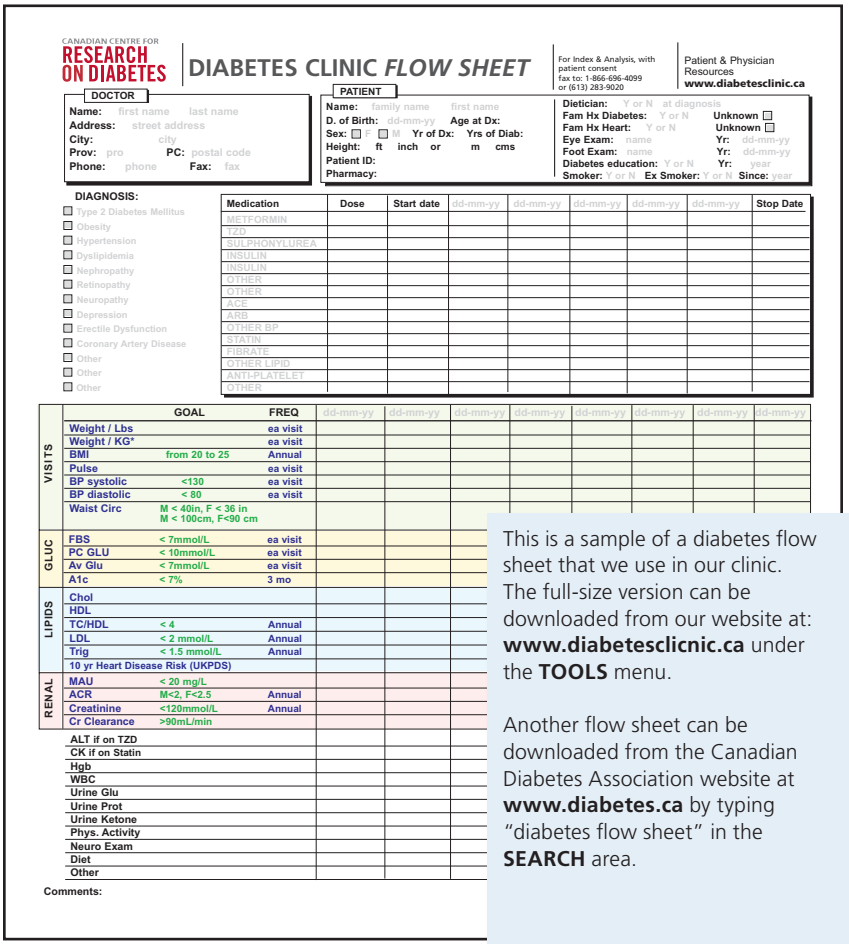
- ☐ In individuals with IGT, a structured program of lifestyle modification that includes modest weight loss and regular physical activity should be implemented to reduce the risk of type 2 diabetes. Pharmacologic therapy with metformin, a TZD, the combination of rosiglitazone and metformin, or acarbose may also be considered
- ☐ People age 40 and over should be screened with an FPG every 3 years. In people with risk factors (e.g. family history, history of GDM, obesity, high-risk ethnicity, evidence of complications, hypertension, dyslipidemia, prediabetes), more frequent and and/or earlier screening should be considered.
- ☐ A1C is the preferred measurement of long-term glycemic control and should be done every 3 months with a target of ≤7.0% for most patients (or ≤6.5% if safely achievable, particularly with recent onset of diabetes or to prevent microvascular complications). An A1C of 6.0 to 6.5% is associated with preiabetes and an A1C >6.5% is associated with diabetes.
- ☐ The first priority in the prevention of diabetes-related complications is reduction of CV risk.
- ☐ The BP target for all people with diabetes is ≤130/80 mm Hg.
- ☐ Vascular protection should also include BP, glycemic and lipid control, lifestyle modifications and smoking cessation, and possibly ASA therapy (as indicated).
- ☐ ACE inhibitor or ARB therapy, as part of a multifaceted approach to vascular protection, is often indicated for people with diabetes. This is particularly important in people with increased vascular risk, such as those with hypertension or elevated microalbuminuria.
- ☐ Guideline-recommended lipid targets for most people with diabetes are low-density lipoprotein cholesterol (LDL-C) ≤2.0 mmol/L and total cholesterol to HDL-C ratio (TC/HDL-C) <4. A statin is indicated in people with diabetes with high CV risk, targeting an LDL-C ≤2.0 mmol/L or a 50% LDL-C reduction.
- ☐ Microalbuminuria is an independent risk factor for CVD, and a potent predictor of nephropathy and mortality.
- ☐ Screening for neuropathy can be performed quickly and reliably with a 10-g monofilament.
- ☐ A dilated eye exam by an eye specialist should be done at diagnosis of type 2 diabetes and every 2 years.
- ☐ At diagnosis of type 2 diabetes, patients should receive counselling from a registered dietitian and should receive diabetes education.

Once the diagnosis of type 2 diabetes is made:

NOW WHAT?

1. Organize your diabetes care

Diabetes care should be organized around the patient using an interdisciplinary team approach. The diabetes healthcare team should provide systematic and coordinated care that establishes and maintains communication with the necessary healthcare and community resources. Use of a diabetes flow sheet can improve care.



CANADIAN CENTRE FOR RESEARCH ON DIABETES

DIABETES CLINIC *FLOW SHEET*

For Index & Analysis, with patient consent fax to: 1-866-696-4099 or (613) 283-9020

Patient & Physician Resources **www.diabetesclinic.ca**

DOCTOR
Name: first name last name
Address: street address
City: city
Prov: pro PC: postal code
Phone: phone Fax: fax

PATIENT
Name: family name first name
D. of Birth: dd-mm-yy Age at Dx:
Sex: F M Yr of Dx: Yrs of Diab:
Height: ft inch or m cms
Patient ID:
Pharmacy:

Dietician: Y or N at diagnosis
Fam Hx Diabetes: Y or N Unknown
Fam Hx Heart: Y or N Unknown
Eye Exam: name Yr: dd-mm-yy
Foot Exam: name Yr: dd-mm-yy
Diabetes education: Y or N Yr: year
Smoker: Y or N Ex Smoker: Y or N Since: year

DIAGNOSIS:
- Type 2 Diabetes Mellitus
- Obesity
- Hypertension
- Dyslipidemia
- Nephropathy
- Retinopathy
- Neuropathy
- Depression
- Erectile Dysfunction
- Coronary Artery Disease
- Other
- Other
- Other

Medication	Dose	Start date	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy	Stop Date
METFORMIN								
TZD								
SULPHONYLUREA								
INSULIN								
INSULIN								
OTHER								
OTHER								
ACE								
ARB								
OTHER BP								
STATIN								
FIBRATE								
OTHER LIPID								
ANTI-PLATELET								
OTHER								

		GOAL	FREQ	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy	dd-mm-yy
VISITS	Weight / Lbs		ea visit								
	Weight / KG*		ea visit								
	BMI	from 20 to 25	Annual								
	Pulse		ea visit								
	BP systolic	<130	ea visit								
	BP diastolic	< 80	ea visit								
	Waist Circ	M < 40in, F < 36 in M < 100cm, F<90 cm									
GLUC	FBS	< 7mmol/L	ea visit								
	PC GLU	< 10mmol/L	ea visit								
	Av Glu	< 7mmol/L	ea visit								
	A1c	< 7%	3 mo								
LIPIDS	Chol										
	HDL										
	TC/HDL	< 4	Annual								
	LDL	< 2 mmol/L	Annual								
	Trig	< 1.5 mmol/L	Annual								
	10 yr Heart Disease Risk (UKPDS)										
RENAL	MAU	< 20 mg/L									
	ACR	M<2, F<2.5	Annual								
	Creatinine	<120mmol/L	Annual								
	Cr Clearance	>90mL/min									
	ALT if on TZD										
	CK if on Statin										
	Hgb										
	WBC										
	Urine Glu										
	Urine Prot										
	Urine Ketone										
	Phys. Activity										
	Neuro Exam										
	Diet										
	Other										

Comments:

This is a sample of a diabetes flow sheet that we use in our clinic. The full-size version can be downloaded from our website at: **www.diabetesclicnic.ca** under the **TOOLS** menu.

Another flow sheet can be downloaded from the Canadian Diabetes Association website at **www.diabetes.ca** by typing "diabetes flow sheet" in the **SEARCH** area.

2. Stress importance of lifestyle education and modifications

Lifestyle education

- All patients with diabetes should receive healthy lifestyle counselling.
- Referral to a registered dietitian for assessment of dietary practices and development of a meal plan.*
- Referral to a diabetes nurse educator to set goals and educate the patient on increasing activity levels, monitoring blood glucose levels and incorporating diabetes self-care practices into their activities of daily living.

Lifestyle goals

- A weight loss goal of 5 to 10% of initial body weight for obese patients with type 2 diabetes is recommended to improve glycemic and metabolic control.
- People with diabetes should follow *Eating Well With Canada's Food Guide*.
- Patients should be encouraged to accumulate at least 150 minutes of moderate-intensity aerobic exercise each week, spread over at least 3 days of the week.
- Patients should be encouraged to perform resistance exercise 3 times per week.
- Structured physical activity counselling by a physician or skilled healthcare provided is very effective in increasing physical activity.
- An exercise electrocardiogram (ECG) stress test should be considered for previously sedentary individuals with risk factors for CVD who wish to undertake exercise more vigorous than brisk walking.
- Continue to encourage and support smoking cessation.

* A practical resource to help your patient adopt healthier eating habits is the Canadian Diabetes Association publication *Meals for Good Health*, by Karen Graham, RD CDE. It includes life-size photographs of 1200- to 2200-calorie everyday meal plans. Patients can order a copy online at www.mealsforgoodhealth.com

3. Screen for complications

Screening for early complications is indicated at the time of diagnosis of diabetes, as many of those newly diagnosed will or be at risk for complications.[1]

The following tests and examinations are indicated (see p.47 for appropriate screening tests and monitoring intervals):

- Blood glucose
- BP
- Lipid profile
- Dilated eye exam
- Thorough foot exam, including screening for peripheral neuropathy
- Screening for microalbuminuria
- Sexual function history
- Assessment of CV risk factors
- Baseline resting ECG in certain patients

4. Book a follow-up appointment

A follow-up appointment should be made to assess management goals and to adjust therapy as needed. One reason why patients sometimes fail to achieve treatment targets is that we, their healthcare professionals, do not follow up regularly and adjust their treatments as needed. Our patients with diabetes should never leave our offices without a booked follow-up appointment. In the stable patient who is meeting treatment targets, we should follow up and do an A1C approximately every three months. In the patient who is not achieving treatment goals, we may want to follow up more often. It is often helpful to give the patient a lab requisition so the necessary blood work can be done a few days before the next appointment.

MANAGEMENT OF HYPERGLYCEMIA

Optimal management of type 2 diabetes is characterized by early, aggressive treatment that is individualized to each patient and targets the pathophysiologic contributors to type 2 diabetes, insulin resistance, beta cell failure and incretin hormone deficiency.

Glycemic Targets

The 2008 Canadian Diabetes Association's Clinical Practice Guidelines[1] recommend the targets in Table 6. Therapy in most patients with diabetes should be tailored to achieve an A1C ≤7.0% in order to reduce the risk of microvascular complications. Lowering glycemic levels toward ≤6.5% may be considered for patients to further lower the risk of nephropathy, but this must be balanced against the risk of hypoglycemia and risk of mortality in patients at significantly elevated risk of CVD.

Table 6. Recommended targets for glycemic control [1]

A1C* (%)	FPG or preprandial PG (mmol/L)	2-hour postprandial PG (mmol/L)
≤7.0	4.0–7.0	5.0–10.0 (5.0–8.0 if A1C target not being met)

* Treatment goals and strategies must be tailored to the individual with diabetes, with consideration given to individual risk factors.

MONITORING OF GLYCEMIC CONTROL

Awareness of all measures of glycemia, including A1C, fasting and postprandial blood glucose values provides the most complete picture of glycemic control.

Glycated hemoglobin (A1C)

- A1C should be measured approximately every three months to ensure that glycemic goals are being met or maintained.
- Testing at least every six months may be considered in adults during periods of treatment and lifestyle stability when glycemic targets have been consistently achieved.
- **A1C goal: ≤7.0%**

Self-monitoring of blood glucose

- Patients, who are able, should be taught how to self-manage their diabetes, including SMBG.
- The benefits of SMBG may include improved A1C, avoidance of hypoglycemia and increased lifestyle flexibility. These benefits are enhanced when patients are willing to adjust their food intake, exercise activity and medications in response to blood glucose values. SMBG also empowers patients to make their own choices to achieve glycemic control (see Table 7).
- Instruct patients to vary the times at which they test, i.e. sometimes measuring fasting or before meals, or sometimes testing two hours after meals. It is important that both fasting and post-meal testing be done, since the treatment of fasting hyperglycemia (which represents a beta cell defect) and postprandial hyperglycemia (which represents insulin resistance and is a potent predictor of CV mortality) may entail different therapeutic approaches.

Table 7. SMGB goals for most patients

Fasting or before meals	2 hours after meals
4.0 to 7.0 mmol/L	5.0 to 10.0 mmol/L (5.0 to 8.0 mmol/L if A1C targets not being met)

Frequency of SMBG

The frequency of SMBG should be tailored to the patient's level of glycemic control and type of therapy.

- **For individuals using intensive insulin:** at least three times daily, including both pre- and postprandial measurements.
- **For individuals on once-daily insulin in addition to oral agents:** at least once per day usually in the morning with supplemental measurements at variable times.
- **For individuals treated with oral agents or lifestyle alone:** frequency should be individualized depending on glycemic control and type of therapy and should include both pre- and postprandial measurements.

In many situations more frequent testing may be required to make treatment decisions to achieve glycemic targets or avoid hypoglycemia.

Accuracy of SMBG

At least annually (and whenever indicators of glycemic control do not match meter readings), a correlation between the glucose meter and a laboratory plasma glucose should be done. Ask patients to take their meter when they go to have lab work done. Have them check their capillary glucose within five minutes of getting the lab glucose tested and write the result in their diary. When they come in to review the lab work, the correlation with the meter can also be reviewed. If the meter and lab value are more than 20% apart, the meter should be checked with a test solution of known glucose concentration provided by the meter manufacturer (the pharmacy can usually do this).

If the discrepancy persists, the patient should contact the meter manufacturer or pharmacy, who will generally provide a replacement meter. All modern meters offer accuracy and reproducibility, so the patient should choose the meter that works best for him or her. Inaccuracies are most commonly due to failure to correctly code for the strips or outdated strips. Many of the modern glucose meters do not require coding. Glucose test strips that have been left open may also give inaccurate results; thus, strip containers should be closed between uses.

Ketone testing

Diabetic ketoacidosis (DKA) is a potentially life-threatening situation and can occur in patients with type 2 diabetes. If all of the following conditions are present, patients should consider ketone testing:

- acute illness, and
- preprandial blood glucose levels >14.0 mmol/L, and
- symptoms of DKA (nausea, vomiting, abdominal pain).

While urine tests for ketones may be used, it is preferable to use a meter that tests blood levels of beta-hydroxybutyric acid (e.g. Precision Extra).

DKA is a medical emergency and has a high mortality rate; thus, if blood glucose values are high and ketones are present, immediate medical care should be sought.

» High blood glucose with ketones is a medical emergency «

Pharmacotherapy

Figure 1 summarizes the guideline-recommended approach to the management of hyperglycemia in type 2 diabetes.

General principles

- **Initiate lifestyle modifications in all patients:** While lifestyle remains a cornerstone of diabetes treatment, many patients find it difficult to maintain the necessary changes over the long term. Although lifestyle modifications have overall health benefits, they are often not sufficient to lower blood glucose to target. Therefore, do not rely on lifestyle measures alone for more than two or three months.
- **If A1C is <9.0%:** Initiate metformin at the same time as lifestyle measures.
- **If A1C is ≥9.0%:** Start pharmacologic therapy concomitantly with lifestyle modifications. Consider initiating metformin with another agent from different class or insulin. Most oral agents have the potential to lower A1C by about 1.0 to 1.5%. Thus, if initial A1C is ≥9.0%, initial combination therapy should be considered targeting insulin resistance and insulin sensitivity.
- **If A1C is ≥9.0 with symptomatic hyperglycemia and metabolic decompensation:** Consider initiating insulin with or without metformin.
- **If glycemic targets are not met on monotherapy:** an agent(s) from another class should be added. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that two, if not three, different agents in combination will frequently be required.[18] Adding a drug from another class of agents often addresses the progressive nature of hyperglycemia.
- The initial use of combinations of **submaximal doses**, compared with monotherapy at the maximum dose, results in more rapid and better glucose control without a significant increase in side effects. Oral agents of one class may be combined with agents of another class and/or insulin. **Do not combine drugs in the same class, such as a sulfonylurea with a meglitinide.**
- The **lag period** between adding antihyperglycemic agents should be kept to a minimum, with consideration given to the pharmacokinetics of the agents used in order to achieve glycemic control with A1C ≤7.0% within six months.

Management of hyperglycemia in type 2 diabetes

Clinical Assessment

Lifestyle intervention (initiation of nutrition therapy and physical activity)

A1C < 9.0%	A1C ≥ 9.0% and physical activity	Symptomatic hyperglycemia with metabolic decompensation
Initiate metformin	Initiate **pharmacotherapy** immediately without waiting for effect from lifestyle interventions: • Consider initiating **metformin** concurrently with another agent from a different class; or • Initiate **insulin**	Initiate insulin ± metformin

If not at target

Add an agent best suited to the individual based on the advantages/disadvantages listed below and the information contained in Tables 8 and 9 (agents listed in alphabetical order)

Class	A1C	Hypoglycemia	Other advantages	Other disadvantages
Acarbose	↓	Rare	Improved postprandial control Weight neutral	GI side effects
Incretin agent: DPP-4 inhibitor	↓ to ↓↓	Rare	Improved postprandial control weight neutral	New agent (unknown long-term safety)
Insulin	↓↓↓	Yes	No dose ceiling Many types, flexible regimens	Weight gain
Insulin Secretagogue:				
- Meglitinide - Sulfonylureas	↓ to ↓↓↓ ↓↓	Yes* Yes	Improved postprandial control Newer sulfonylureas (gliclazide, glimepiride) are associated with less hypoglycemia than glyburide	Requires TID to QID dosing Weight gain
TZD	↓↓	Rare	Durable monotherapy	Requires 6-12 weeks for maximal effect Edema, rare CHF, rare fractures in females
Weight loss agent	↓	Rare	Weight loss	GI side effects (orlistat) Increased heart rate/BP (sibutramine)

If not at target

- Add another drug from a different class or
- Add bedtime basal insulin to other agent(s) or
- Intensify Insulin regimen

Timely ajustments to and/or addition of anthyperglycemic agents should be made to attain target A1C within 6 to 12 months

* Less hypoglycemia in the context of missed meals. Reproduced with permission from CDA [1].

Table 8. Mechanism of action of oral antihyperglycemic medications

Medication	Mechanism of action
Metformin	Acts mainly by reducing hepatic glucose production, and is indicated in the presence of fasting hyperglycemia. Exerts some effect on skeletal muscle by enhancing glucose uptake (though the mechanism of this action is not well known) and increasing insulin sensitivity.
Thiazolidinediones (e.g. pioglitazone, rosiglitazone)	Through the activation of the nuclear receptor PPAR-gamma, diminish insulin resistance (especially in the muscles and adipose tissue) and, at higher doses, in the liver.
Acarbose	Inhibits the breakdown of disaccharides and polysaccharides (starch) to glucose in the duodenum, thus slowing absorption of glucose and decreasing postprandial hyperglycemia. Allows the pancreas to dispose of the postprandial glucose load over a longer period of time. Slows absorption of carbohydrate.
Sulfonylureas (e.g. gliclazide, glyburide)	Stimulate insulin secretion through the modulation of potassium channels in pancreatic beta cells.
Non-sulfonylurea insulin secretagogues (e.g. nateglinide, repaglinide)	Similar to sulfonylureas in their mechanism of action, however, have a briefer and more immediate effect.
GLP-1 agonists (e.g. exenatide, liraglutide)	Mimic the actions of endogenous GLP-1 to address the imbalance. The incretin effect describes the difference in insulin secretion observed when people are administered glucose orally vs. by infusion. The difference in the incretin effect between normal controls and patients with type 2 diabetes is attributed to an impaired action of gut hormones (incretins), such as GLP-1 and GIP.
DPP-4 inhibitors (e.g. sitagliptin, saxagliptin)	Inhibit the action of DPP-4 and increase levels of GLP-1, thereby increasing postprandial insulin secretion in a glucose-dependant manner by up to 60%, (assuming a functioning beta cell). They also decrease glucagon secretion by the alpha cells of the pancreas, thereby decreasing new glucose formation by the liver.

Table 9. Factors to consider when choosing a pharmacologic treatment regimen

- Level of glycemia and presence of symptoms of diabetes
- Age of the patient
- Predominance of insulin resistance or insulin deficiency
- Renal and hepatic function
- Presence or risk of CVD
- Concomitant pharmacotherapy for other health conditions
- Motivation to reach target levels
- Psychosocial deficits that may impact medication administration or safety
- Ability to pay
- Side effects of medications (e.g. risk of hypoglycemia or GI distress)
- Possible multiple beneficial effects of certain medications

The mechanism of action of each oral agent is listed in Table 8 (p. 18).

METFORMIN

Metformin can cause gastric discomfort and diarrhea, and has been associated with lactic acidosis in the presence of renal or hepatic dysfunction. It is taken with meals (usually with breakfast and supper) in order to decrease gastric irritation. Metformin is not associated with weight gain and works particularly well with a TZD or incretin therapy. It does not cause hypoglycemia, and may be used with insulin. Metformin lowers A1C by 1% to 2%, may confer some CV benefits and is cost effective.

Metformin (Glucophage)

Tablets: 500 mg and 850 mg

Starting dosage: ½ a 500-mg tablet daily

Titration/dosing: Titrate to a maximum dosage of 2.5 g/day. Very little additional benefit at doses >1500 mg/day. The maximal therapeutic dose is usually 2000 mg/day, and at doses above this, there is reduced efficacy.[19]

Slow-release metformin (Glumetza)

Tablets: 500 mg and 1000 mg

Starting dosage: 1000 mg OD

Titration/dosing: Titrate to a maximum dosage of 2 g OD (2 x 1000 mg QD). Recommended once daily with the evening meal. Very little additional benefit at dosages >2000 mg/day.

THIAZOLIDINEDIONES (TZDS OR GLITAZONES)

A TZD may be used as monotherapy in patients in whom metformin is inappropriate because of contraindications or intolerance. As dual therapy, TZDs are indicated in combination with metformin or with a sulfonylurea when monotherapy with metformin or sulfonylurea does not result in adequate glycemic control or these drugs are contraindicated.

Importantly, full effectiveness of TZDs may not be achieved for up to 12 weeks. It is important to encourage adherence to therapy, regardless of early lack of observable benefit. Utilizing endogenous insulin, the patient using a TZD will not experience hypoglycemia.

These drugs may induce mild edema or fluid retention, which may be

reduced with diuretics (amiloride or spironolactone are most effective). Do not use in patients with congestive heart failure (CHF) (NYHA Class I to IV). Discontinue immediately if CHF develops. When used in combination with insulin (not currently an approved indication in Canada), may increase the risk of edema or CHF. TZDs are not recommended in patients with active liver disease. Only if symptoms warrant should follow-up liver function tests be performed. Preservation of pancreatic beta cell function is a feature of TZD treatment; in the DREAM trial,[13] rosiglitazone decreased the progression of prediabetes to diabetes by approximately 60%. The ADOPT study[20] showed rosiglitazone had the longest period of time before monotherapy failure and the PROACTIVE trial[21] showed prolongation of the time to insulin requirement with pioglitazone.

Although a meta-analysis in 2006[22] suggested that rosiglitazone may increase risk of myocardial infarction (MI), subsequent trials including RECORD,[23] ACCORD,[24] ADVANCE[25] and BARI-2D[26] did not show signs of increased risk. Nonetheless the controversy over Avandia has continued and in September 2010, the European Medicines Agency removed the drug from the European market. At the same time, the United States Food & Drug Administration restricted the use of Avandia to those people who were already stable on the drug or for those who could not tolerate other alternatives. Pioglitazone has become the preferred drug, although there are other dual PPAR agonists in development.

Rosiglitazone (Avandia)

Tablets: 2 mg, 4 mg, 8 mg

Starting dosage: Usual starting dosage is 4 mg OD

Titration/dosing: Increase to 8 mg in 3 months if glycemic goals have not been reached. Dosage range is 2 to 8 mg/day; 4 mg BID is most effective.

Pioglitazone (Actos) and generics

Tablets: 15 mg, 30 mg, 45 mg

Staring dosage: Usual starting dosage is 30 mg OD

Titration/dosing: Increase to 45 mg in 3 months if needed. Dose range is 15 to 45 mg.

Combination products

Avandamet (Avandia [rosiglitazone] plus metformin)

Tablets: 2/500, 2/1000, and 4/1000 mg (2 or 4 mg rosiglitazone with 500 or 1000 mg metformin)

Starting dosage: 2/500 to 2/1000 OD

Titration/dosing: Increase to 4/1000 mg BID

Avandaryl (Avandia [rosiglitazone] plus glimepiride [a sulfonylurea])

Tablets: 4/1, 4/2, 4/4 mg (4 mg rosiglitazone with 1, 2 or 4 mg glimepiride)

Starting dosage: Usually 4/1 mg OD

Titration/dosing: Titrate according to need for the glimepiride. Maximum dosage is 2 tablets of 4/4 mg per day.

INCRETIN THERAPIES

Incretins are small peptide hormones (glucose dependant insulinotropic peptide [GIP] and glucagon like peptide-1 [GLP-1]) that are secreted by the gut in response to ingestion of food. The incretin hormone that is most involved in glucose regulation is GLP-1, which is secreted by the L cells in the terminal ileum. It is known as an incretin hormone because it acts to "increase" glucose-dependant insulin secretion by the pancreatic beta cell. The "incretin effect" may augment insulin production by up to 60%, but it does so in a glucose-dependant manner so that the higher the glucose level, the greater the increase in insulin production. This protects against hypoglycemia by titrating insulin production to need. Since the incretin effect works only if there is sufficient beta cell function to stimulate, this class of medication is most effective in the early stages of diabetes when there is still some preserved beta cell function. GLP-1 also decreases glucagon secretion by the alpha cells of the pancreas, thereby decreasing glucose production by the liver. There are also central effects of GLP-1 in stimulating the satiety centre in the brain to decrease appetite by signaling increased satiety. There is also a decrease of gastric motility, which slows stomach emptying. The effect of GLP-1 is very short because the hormone is broken down and de-activated by the action of the dipeptylpeptidase (DPP-4) enzyme.

Effects of GLP-1 hormone in glucose regulation

1. Increases glucose-dependant insulin secretion
2. Slows gastric emptying
3. Inhibits glucagon secretion, thereby decreasing glucose production
4. Increases satiety, decreases appetite

GLP-1 levels are decreased in people with diabetes and may be a contributory factor to obesity and postprandial hyperglycemia. Increasing GLP-1 levels may restore glucose homeostasis. In order to increase GLP-1 levels, we can either administer a synthetic GLP-1 analogue, which is not broken down by DPP-4, or augment natural GLP-1 levels by inhibiting the breakdown of the hormone by the DPP-4 enzyme.

DPP-4 inhibitors

Oral medications that inhibit the action of DPP-4 and increase levels of GLP-1, thereby increasing postprandial insulin secretion in a glucose-dependant manner by up to 60%, (assuming a functioning beta cell). They also decrease glucagon secretion by the alpha cells of the pancreas, thereby decreasing new glucose formation by the liver.

These agents are generally approved for addition to metformin and/or sulphonylurea or as montherapy in metformin intolerance. In combination with metformin we expect a 1.5 to 1.5% A1C reduction with no risk of hypoglycemia and minimal side effects. As monotherapy or add-on therapy, the expected A1C reduction is about 0.7%. DPP-4 inhibitors are not approved in pregnancy and should not be used in moderate to severe renal failure (eGFR <30 mL/min). The effects of slowed gastric emptying and the central effect of increased satiety are minimally affected by DPP-4 inhibitors, but there may be modest weight loss or at least no weight gain.

Sitagliptin (Januvia)

Januvia is marketed by Merck in Canada. It is indicated in patients with type 2 diabetes to improve glycemic control in combination with metformin, when metformin alone does not provide adequate glycemic control or as an adjunct to diet and exercise as monotherapy when metformin is inappropriate due to contra-indications or intolerance. Expected A1C reduction is about 0.7% when added to metformin. It is not indicated in patients with moderate to severe renal failure (eGFR <30 mL/min). The medication is well tolerated with a low rate of side effects and very low risk of hypoglycemia when given alone or with metformin.

Tablets: 100 mg
Starting dose: 100 mg OD
Titration/dosing: No titration. Maximum dosage 100 mg OD.

Saxagliptin (Onglyza)

Onglyza is marketed in Canada by AstraZeneca and Bristol-Myers Squibb. It is indicated in patients with type 2 diabetes to improve glycemic control in combination with metformin or a sulfonylurea, when metformin or sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control. Expected A1C reduction is about 0.7% when added to metformin or sulfonylurea. It is not indicated in patients with moderate to severe renal failure (eGFR <30 mL/min).
The medication is well tolerated with a low rate of side effects and very low risk of hypoglycemia when given alone or with metformin.

Saxagliptin (Onglyza)

Tablets: 5 mg

Starting dosage: 5 mg OD

Titration/dosing: No titration. Maximum dosage 5 mg OD.

Combination product

Janumet (Januvia [sitagliptin] and metformin)

Tablets: 50/500, 50/850 or 50/1000 mg

Starting dosage: 50/500 mg BID. Start low to avoid GI distress caused by metformin.

Titration/dosing: To 50/850 or 50/1000 mg BID (do not exceed 50/1000 mg BID)

GLP-1 Analogues

Injectable synthetic analogues of GLP-1 that have the metabolic action of GLP-1, but are not inactivated by DPP-4.

Liraglutide (Victoza)

A GLP-1 analogue, 97% homologous to human GLP-1, developed by NovoNordisk. The action is prolonged by conjugation to a C-16 fatty acid palmitoyl, which provides resistance to degradation by DPP-4. The half-life is 13 hours, thus allowing once-daily injection. Major side effect is dose-dependant nausea that tends to improve over a week or so. Weight loss is also a frequent side effect. Expected A1C reduction is about 1.2%. Liraglutide is indicated if target levels of A1C cannot be achieved on metformin alone or in combination with sulfonylurea. Since weight loss is frequently a feature, it has particular value in the obese patient. As with all incretin therapies the patient needs to have a functioning beta cell, so it is best used in early stages of diabetes and has little effect if there is markedly reduced insulin production.

Administration: Once-daily injection with a proprietary disposable pen device

Doses: 0.6 mg, 1.2 mg, 1.8 mg

Starting dosage: 0.6 mg OD

Titration: Increase to 1.2 mg OD after two weeks, which may be increased to 1.8 mg OD if needed. If nausea develops, decrease the dose to the previous level. Not recommended in moderate to severe renal insufficiency (eGFR <30 mL/min).

GLP-1 Mimetics

Drugs that, although chemically distinct from GLP-1, have structural similarities that allow binding to the GLP-1 receptor.

Exenatide (Byetta)

Marketed by Eli Lilly. Side effects include nausea and weight loss. Expected A1C reduction 0.7-1.0%. Use as add on to metormin, best effect in the early stages of diabetes when there is still well-preserved beta cell function. Nausea is a frequent side effect. Do not use in moderate or severe renal insufficiency (eGFR <30 mL/min).

Administration: Twice-daily injection with a proprietary disposable pen device for each dose

Doses: 5 mcg, 10 mcg

Starting dosage: 5 mcg BID

Titration: To 10 mcg BID

INSULIN SECRETAGOGUES

Long-acting (sulfonylureas) and short-acting (meglitinides). Act by stimulating the pancreatic beta cell to produce more insulin. In order for these to be effective there has to be a functioning beta cell, they are; therefore, most effective in the early stages of diabetes when there is still reasonable beta cell function.

Sulfonylureas

Act mainly by increasing insulin production by closing the K-ATP channel in the beta cell.

Glyburide (DiaBeta) and generic

Non-selective and increases insulin output regardless of glucose levels, thus may cause severe and prolonged hypoglycemia, especially in the elderly. Should not be used in moderate or severe renal insufficiency (eGFG < 30 mL/min).

Tablets: 2.5 mg, 5 mg

Starting dosage: 2.5 mg OD

Titration/dosing: Maximum dosage is 10 mg BID. Dosage range is 1.25 to 20 mg/day. Usual dosage is 5 to 10 mg BID. Dosages above 15 to 20 mg/day may confer no further benefit.

Gliclazide (Diamicron, Diamicron MR)

Associated with less hypoglycemia than glyburide, thus more suitable for the elderly. Insulin release is at least partly glucose dependant. Restores first-phase insulin release secretion. No dose adjustment needed in the elderly or those with mild to moderate renal failure (eGFR of 15 to 80 mL/min).

Gliclazide (Diamicron) and generics

Tablets: 80 mg

Starting dosage: 40 to 80 mg BID

Titration/dosing: Dosage range 40 to 360 mg/day, given in divided dose BID

Gliclazide extended release (Diamicron MR) and generics

Once-daily formulation providing 24-hour glucose control. Each 30-mg MR tablet has the therapeutic equivalency of a regular 80-mg Diamicron tablet.

Tablets: 30 mg

Starting dosage: 30 mg OD in the morning

Titration/dosing: Dosage range 30 to 120 mg daily. Titrate to maximum of 120 mg (i.e. 1 to 4 tablets) as 1 dose/day.

Glimepiride (Amaryl) and generics

Once-daily preparation gives 24-hour control. Insulin secretion may be more glucose dependant. Dual elimination by kidney and liver, so may be used in renal failure.

Tablets: 0.5 mg, 1 mg, 2 mg, 4 mg

Starting dosage: 1 mg OD

Titration/dosing: Dosages range from 0.5 to 8 mg/day

Meglitinides

Very short-acting insulin secretagogues, taken with meals. Cause less hypoglycemia than sulfonylureas as the on/off action is very rapid in the postprandial phase. Useful in those in whom meals are irregular, such as the elderly and shift workers, and in people with predominantly postprandial hyperglycemia. Adherence can be a challenge, requiring reinforcement to encourage the patient to take with every meal.

Repaglinide (GlucoNorm)

Tablets: 0.5 mg, 1 mg, 2 mg

Starting dosage: 0.5 mg taken with meals

Titration/dosing: Dosages range from 0.5 to 4 mg before each meal

Nateglinide (Starlix)

Insulin release is glucose dependant.
Tablets: 120 mg
Starting dosage: 120 mg with each meal
Titration/dosing: 120 mg with each meal

ACARBOSE (GLUCOBAY)

Inhibits the breakdown of disaccharides and polysaccharides (starch) to glucose in the duodenum, thus slowing absorption of glucose and decreasing postprandial hyperglycemia. Allows the pancreas to dispose of the postprandial glucose load over a longer period of time. Slows absorption of carbohydrate. Effective for postprandial hyperglycemia. Lowers A1C by about 0.5%. Useful in patients with prediabetes, as it can reduce conversion from IGT to diabetes by 25%. May also be useful in reactive hypoglycemia. High incidence of GI side effects (flatulence and diarrhea), which can be lessened if titrated slowly.

Tablets: 50 mg, 100 mg
Starting dosage: 25 mg with the first bite of each meal
Titration/dosing: Dosage needs to be titrated gradually from 25 to 100 mg to 50 or 100 mg TID with the first bite of each meal. To avoid side effects, start with a low dose and titrate slowly.

ANTI-OBESITY AGENT

Orlistat (Xenical)

Approved for the treatment of type 2 diabetes accompanied by obesity. May be used as an adjunct in the obese. Given with each meal. Adherence to a low-fat diet is very important because the drug inhibits fat absorption. With a high-fat diet, loose fatty stools or fecal incontinence may occur. Lowers A1C by about 0.5%.
Tablets: 120 mg
Starting dosage: One tablet with the largest meal of the day
Titration/dosing: Increase to 1 tablet with each meal

COMBINED ORAL AGENT FORMULATIONS

There are some agents currently available on the market that incorporate two agents into one pill. This approach has been used with antihypertensive and lipid control agents and brings together logical, commonly used combinations of agents. Reducing the number of pills that a patient takes may enhance adherence (see Adherence to Medication Regimens, p. 50); moreover, since a fixed combination may incur only one dispensing fee, there may be cost savings. Currently available combinations in Canada are:

Avandamet (Avandia [rosiglitazone] plus metformin)
Available in 2/500, 2/1000, and 4/1000 mg dose tablets. Usually given twice a day.

Avandaryl (Avandia [rosiglitazone] plus Amaryl [glimepiride])
Available in 4/1, 4/2 and 4/4 mg dose tablets. Given once or twice a day.

Janumet (Januvia [sitagliptin] plus metformin)
Available in 50/500, 50/850 or 50/1000 mg tablets Given twice a day.

RATIONALE FOR USE OF INSULIN

At the time of diagnosis of diabetes, it is estimated that insulin-producing ability has already declined to below 50% of normal. With the inevitable and continuous deterioration of beta-cell function, hyperglycemia becomes more severe.[27] The point at which insulin should be added to the treatment regimen varies from one person to another; generally, if appropriate treatment and lifestyle changes are implemented, good glycemic control may be maintained with insulin production as low as 20% of normal. There comes a point, however, where introduction of exogenous insulin is required to prevent metabolic decompensation. Insulin should not be seen as a drug of last resort. Patients with high A1C and/or longstanding glycemic values above target should be considered for insulin therapy (added to oral agents or in place of oral agents). Initially, the use of insulin is fairly simple; one of many regimens can be used because precise replacement is not needed but rather a correction of some of the relative insulin deficit. In the earlier stages; when glycemic control with A1C ≤7.0% (estimated average glucose [eAG] 8.6 mmol/L [see Table 10][28]) can no longer be achieved with oral antihyperglycemic agents, the CDA guidelines recommend addition of insulin. As time passes and endogenous insulin production declines still further to minimal levels, more intensive insulin replacement regimens are needed, including basal/bolus insulin therapy.

Table 10. Estimated average glucose [28]

A1C (%)	mmol/L*
5	5.4 (4.2–6.7)
6	7.0 (5.5–8.5)
7	8.6 (6.8–10.3)
8	10.2 (8.1–12.1)
9	11.8 (9.4–13.9)
10	13.4 (10.7–15.7)
11	14.9 (12.0–17.5)
12	16.5 (13.3–19.3)

*Data in parentheses are 95% confidence intervals.

If adequate glycemic control (A1C ≤7.0%) cannot be maintained on oral agents alone, insulin should be added.

OVERCOMING RESISTANCE TO USE INSULIN

Many physicians and patients alike resist the initiation of insulin. It is important to overcome this barrier. With the progressive decline in insulin production, individuals who have had diabetes for eight to 10 years most often need addition of insulin in order to achieve glycemic control since their endogenous insulin production has declined to very low levels. Patients who are not initially motivated should be encouraged to try insulin. Sometimes it may be preferable to introduce insulin as a temporary trial with the understanding that if the patient does not feel better on insulin, a return to previous treatment is possible. It is essential to explain the many benefits of good glucose control and to make insulin initiation as simple as possible. Even patients who are not physically able (such as nursing home residents) can do very well on insulin administered by a caregiver.

INSULIN BASICS: Basal, bolus, premixed insulins

Basal insulin

Insulin is involved in glucose transfer across cell membranes in order to provide the energy required for metabolism. Thus, we need some constant supply of insulin to provide glucose to the tissues for the activities of staying alive (breathing, heartbeat, brain activity, etc). This constant supply is known as basal insulin. In type 1 diabetes, where there is no endogenous insulin production, about 50% of daily insulin needs are for basal insulin. In type 2 diabetes, where there is some endogenous insulin, basal needs may be lower. A fairly continuous basal insulin release is desirable.

Exogenous basal insulin needs can be supplied by:

- **A long-acting insulin analogue** (glargine [Lantus] or detemir [Levemir]) given once a day. With virtually constant insulin action for up to 24 hours, these insulins provide the closest to an ideal basal insulin supply. Since these insulins have minimal activity peak, they also cause less hypoglycemia than NPH. The long-acting basal insulin analogues (insulin glargine [Lantus] or insulin detemir [Levemir]) have a virtually flat profile of action for up to 24 hours. Because of the extended action, the injection may be given at any time of the day, as long as the time is consistent from one day to the next. It may be given whenever the oral medications are taken in order to enhance adherence or to increase flexibility for other healthcare

providers such as home-care nurse. The pharmacokinetics of long-acting insulin analogues are dose-dependant and in some studies the duration of action of detemir (Levemir) is a bit shorter; thus, when very small doses or very large doses are used, twice-daily administration may be preferred or adjusting the timing of once-daily administration. For instance, if insulin is given in the morning and the fasting glucose levels are high in the morning, it may be helpful to change the insulin administration time to evening.

- An intermediate-acting insulin (NPH) given twice a day.

Bolus insulin

Postprandially, insulin removes glucose from the blood and stores it as glycogen and fat. Insulin is needed to reduce postprandial hyperglycemia and increase peripheral glucose utilization. This is known as bolus insulin. In the person with type 2 diabetes, we often see postprandial hyperglycemia, as the pancreas may not be able supply enough insulin to provide for peak postprandial needs.

Postprandial hyperglycemia can be treated by giving a rapid-acting insulin analogue aspart [Novorapid], glulisine [Apidra] or lispro [Humalog] with meals. These insulin analogues have an onset of action in 10 to 15 minutes, peak in 60 to 90 minutes, and have a duration of action two to four hours.

In an intensive MDI insulin regimen, aspart [Novorapid], glulisine [Apidra] or lispro [Humalog] is given with meals in a dose to balance the carbohydrate content of the meal. Dose varies according to the amount of carbohydrate eaten.

The bolus insulin may be taken just before the meal, with the meal, or even just after the meal. The goal is to achieve normal two-hour postprandial values. The carbohydrate-to-insulin match can be judged by a capillary glucose measured two hours after the meal.

Premixed insulins

Some physicians have a comfort level with premixed insulins. These insulins are usually used twice daily. For example, a 30/70 human insulin mixture (Humulin 30/70 or Novolin GE 30/70) is given as two-thirds of the total daily dose in the morning and one-third with supper. The usual insulin dose is about 0.5 to 1 units/kg. For dose adjustment, concentrate on correcting the highest blood glucose value of the day. This can be accomplished using a dose-adjustment formula (for example, increase the dose by 2 units if blood glucose is >10.0 mmol/L for two or three days in a row).

- If morning glucose is high, increase the evening premix dose.
- If evening glucose is high, increase the morning premix.
- If, despite adjustment of morning dose, hypoglycemia occurs in the daytime or A1C is still above target of ≤7.0%, it may help to add a small dose of premix with the midday meal (start with about 6 units). An alternative would be to change to a 50/50 analogue premix, such as Humalog Mix 50 with each meal.

Premixed insulins include the following:

- **Humulin 30/70** (30% regular and 70% NPH);
  available in 3-cc cartridge for Humapen Luxura or 10-cc vial
- **Novolin ge 30/70** (30% regular and 70% NPH);
  available in 3-cc cartridge for Novolin Pen 4 or 10-cc vial
- **Humalog Mix25** (25% rapid-acting insulin analogue [lispro] with 75% Humulin-NPL [NPL, an intermediate-acting insulin]);
  available in 3-cc cartridge for Humapen Luxura or disposable KwikPen
- **Humalog Mix 50** (50% rapid-acting insulin analogue [lispro] with 50% Humulin-NPL [NPL, an intermediate-acting insulin]);
  available in 3-cc cartridge for Humapen Luxura or disposable KwikPen
- **Novomix 30** (30% rapid-acting insulin analogue [aspart] and 70% intermediate-acting insulin analogue NPA (neutral protamine aspart);
  available in 3-cc cartridge for Novolin Pen 4 or disposable FlexPen

A potential problem with premixed insulins given at suppertime is that the intermediate-acting component (NPH, NPL or NPA) peaks about seven or eight hours after administration. This peak may therefore occur at around 2:00 AM, when insulin needs are lowest, and may cause nocturnal hypoglycemia, or may not supply enough insulin to cover the dawn phenomenon from 4:00 to 8:00 AM. If either of these is a problem, we can give a rapid-acting insulin analogue (such as insulin aspart [Novorapid]), insulin glulisine (Apidra) or insulin lispro [Humalog] with supper and the intermediate-acting or long acting insulin at bedtime. This is known as a "basal plus" technique and is a good start to intensifying insulin to multiple daily injections (MDI).

INSULIN REGIMENS

Adding bedtime insulin to daytime oral agents

When lifestyle modification and oral agents are no longer sufficient to maintain A1C in the target range (A1C ≤7.0%), the addition of intermediate-acting insulin (NPH) or an long-acting insulin analogue (glargine [Lantus] or detemir [Levemir]) at bedtime may achieve better blood glucose levels in the morning,

thereby decreasing glucose toxicity and allowing the daytime oral agents to be more effective. The long-acting insulin analogues (glargine [Lantus] or detemir [Levemir]) last 24 hours, so they may be given at any time of the day (though the time should be consistent from one day to the next). There is less risk of hypoglycemia using a long-acting analogue compared with NPH. Frequently in type 2 diabetes, the highest glucose value of the day is the fasting value. This is primarily caused by overnight hepatic glucose production. The administration of exogenous insulin suppresses glucagon secretion and thereby decreases overnight glucose formation by the liver.

The dawn phenomenon, characterized by increased steroid levels (particularly growth hormone), further increases morning glucose levels. Hepatic glucose production is sensitive to suppression by insulin. Thus, a small dose of insulin at night, may suppress hepatic glucose output and achieve a lower fasting glucose level. The dose required at night to suppress hepatic glucose production is lower than the dose required to stimulate peripheral glucose uptake to treat postprandial hyperglycemia and is usually safe with little potential to cause hypoglycemia.

» Self-monitoring of blood glucose is an important component of insulin therapy. «

Advantages of bedtime insulin

Bedtime basal insulin is a good starting point for patients who may need multiple injections later, as it allows them to become comfortable with the injections and the concept of insulin adjustment to achieve a glycemic goal. Other advantages include:

- Safe, less likely to cause overnight hypoglycemia (especially with glargine [Lantus] and detemir [Levemir])
- Easy to teach
- Only one injection/day
- Small doses of insulin are needed, causing less weight gain
- Can be given by insulin pen (simple, virtually painless, no mixing needed)

General principles of bedtime insulin adjustment

Since hyperinsulinemia is associated with weight gain and increases the risk of hypoglycemia, we want to use the smallest possible dose of insulin to achieve our objective of a normal fasting glucose level. We get almost as good A1C reduction with less risk of hypoglycemia using a small dose of insulin at night to suppress overnight glucose production by the liver than by giving daytime insulin to increase glucose disposal.

Goal: To achieve stable fasting blood glucose values of 4.0 to 7.0 mmol/L

Dose: 0.1 to 0.3 units/kg or 1 unit/mmol/L of fasting blood glucose (i.e. if usual fasting glucose is 13 mmol/L, the required insulin dose would be about 13 units).

Starting dose: 10 units of insulin administered just before bedtime.
Some can get by with even smaller doses if insulin sensitive. In slim patients or those who live alone, I will often start with a dose of 6 units.

SMBG: Patient should monitor fasting blood glucose daily.

Titration: Increase the dose by 1 or 2 units after three successive days if fasting blood glucose is >7.0 mmol/L. Proceed slowly in trying to achieve the fasting target. Many patients have been hyperglycemic for a long time and may have hypoglycemia symptoms with glucose levels in the normal range (i.e. <4.0 to 6.0 mmol/L). Take your time to correct hyperglycemia. Patients hate hypoglycemia. They feel terrible and simply will not adhere to insulin therapy if we push glucose levels down too fast. Patients gradually become accustomed to normal glucose levels and over time will develop tolerance for levels that previously made them feel hypoglycemic (even though their values were in the normal range).

Reduce bedtime insulin dose by 2 units after an episode of nocturnal hypoglycemia or two successive days with a fasting glucose level <4.0 mmol/L.

An alternate titration method that I have found very successful is to start with a dose of about 10 units of long-acting insulin; then, titrate upward by 1 unit every day that the fasting glucose is >5.5 mmol/L, stop the titration if nocturnal hypoglycemia develops. The advantage of this method is that it is simple and that we titrate to a normal glucose level. If we can get the fasting glucose between 4.0 and 5.5 mmol/L then we are more likely to achieve target

levels of A1C than if we stop our titration at a fasting level of ≤7.0 mmol/L. If we achieve fasting levels <5.5 mmol/L and A1C remains elevated, then we have postprandial hyperglycemia and we then need to add prandial (mealtime) insulin on top of the basal. Often we can start the prandial insulin with one mealtime injection of short-acting analogue at the largest meal of the day. If we still fail to achieve A1C target of ≤7.0% then we will need basal once a day plus prandial insulin with each meal.

Once a stable average fasting glucose level of 4.0 to 7.0 mmol/L has been achieved for a month or so, turn your attention to the pre-lunch, pre-supper and pre-bedtime glucose levels. If these are normal, and A1C is ≤7.0% then we have achieved our goal.

If the patient has normal fasting values, but develops daytime or evening hypoglycemia, reduce the sulfonylurea or the meglitinide (Gluconorm or Starlix). These drugs cause insulin release from the pancreas and may cause hypoglycemia (although this is rare with repaglinide or nateglinide, as these are taken only with meals).

Metformin, TZDs or acarbose on their own do not cause hypoglycemia. If daytime hyperglycemia persists despite full therapeutic doses of appropriate oral agents, we have to consider adding daytime insulin or discontinuing oral agents and using insulin alone.

After a month on a low (introductory) dose of insulin, if the patient is comfortable and willing and is monitoring well, give instructions on how to self-adjust the insulin dose according to SMBG levels (see sample patient instructions on p. 37). Insulin requirements are rarely static, so the patient really needs to become familiar and comfortable with insulin adjustments.

If these measures do not achieve control (A1C ≤7.0%) after three months, referral to a diabetes clinic or diabetes specialist should be considered.

Set limits on insulin adjustments. Remember that some patients will not respond adequately because of profound insulin resistance and will need more frequent insulin therapy. It is not wise to increase insulin doses indefinitely. Patients should not increase the insulin dose to more than 30 units without first reviewing their diary with the physician or diabetes educator. Some patients do need large doses, but beware of overnight hypoglycemia.

REMEMBER

- Don't give up until A1C is in the target range of ≤7.0%.
- Normal fasting or preprandial glucose is 4.0 to 7.0 mmol/L
- Target fasting glucose is ≤7.0 mmol/L. If A1C target is not achieved then titrate to fasting glucose <5.5 mmol/L.
- Target postprandial glucose is 5.0 to 10.0 mmol/L.
- If A1C remains >7.0%, target postprandial glucose 5.0 to 8.0 mmol/L.
- Talk to your patients about their diet and exercise habits, and encourage improvements.

Sample patient instructions
for self-adjustment of bedtime insulin

How to adjust your bedtime insulin dose

I have given you a prescription for:_____

I am giving you a small dose of evening insulin to prevent your blood glucose (sugar) from going too high during the night, so that you will have a normal blood glucose level when you get up in the morning. It is safe and rarely causes low blood glucose (hypoglycemia).

It is very important to measure your blood glucose with your blood glucose meter. You should do this at bedtime before you take your insulin, and in the morning before you eat breakfast. While you are adjusting your insulin, you should also measure and record (in your diary or logbook) your blood glucose readings before lunch and supper as often as possible.

- Start with a dose of 10 units of insulin at bedtime.
- Measure your blood glucose every morning before breakfast.
- If your before-breakfast glucose value is higher than 7.0 for three days in a row, you should increase your bedtime insulin dose by 2 units (that is, from 10 units to 12 units).
- Whenever you have a glucose level higher than 7.0 for three days in a row, you will increase your bedtime insulin by 2 units.
- You should consider testing your blood glucose at 3:00 AM occasionally to ensure you are not having low overnight blood glucose levels.
- Do not go above a daily dose of 30 units of insulin without discussing with me. Your goal is to achieve before-breakfast glucose levels between 4.0 and 7.0 mmol/L.
- If you have a low blood glucose (hypoglycemic) reaction during the night, decrease the bedtime insulin dose by 2 units.
- If you have a before-breakfast glucose reading below 4.0 for two days in a row, decrease the bedtime insulin dose by 2 units.

If you have any problems or questions, please check the information on the web site (www.diabetesclinic.ca) or call me at: _____

For emergencies outside office hours, call: _____

Basal/bolus insulin regimens

Frequently, a more logical approach to insulin therapy is a basal/bolus method (also known as intensive management, multiple daily injections [MDI] or flexible insulin therapy), in which a short-acting (bolus) insulin (aspart [NovoRapid], glulisine [Apidra] or lispro [Humalog]) is given with each meal, and a longer-acting (basal) insulin (NPH, glargine [Lantus] or detemir [Levemir]) is given once or twice a day to maintain a constant basal insulin level.

Basal plus - When basal insulin is not enough

If, despite achieving a normal fasting glucose with adjustment of NPH or long-acting analogue insulin, there is consistent hyperglycemia at certain times of the day, we can alter our insulin therapy to correct these hyperglycemic periods. One technique is to add a single injection of rapid-acting insulin analogue (aspart, glulisine or lispro) with the largest meal of the day. This technique is known as "basal plus" and is a good way to start intensification when basal is not enough.

Intensive insulin therapy – twice daily or multiple daily injections

If, despite achieving a normal fasting glucose with bedtime NPH and maximal therapeutic doses of appropriate oral antihyperglycemic medications, there is still hyperglycemia before lunch and supper, we will likely need to go on twice-daily or intensive insulin treatment. Again, the most logical treatment is MDI. I counsel other physicians that if they are going to learn only one way of giving insulin, this is the one to learn.

Adjusting oral agents

Intensive insulin therapy requires the discontinuation of some oral agents and the initiation of MDI in order to closely mimic the healthy body's basal and bolus insulin secretion patterns. Metformin is usually maintained. Insulin secretagogues (sulfonylurea or meglitinides) are usually discontinued. By the time intensive insulin therapy is required, there is generally very little beta cell function in the pancreas; thus, TZD (rosiglitazone [Avandia] or pioglitazone [Actos])

and incretin therapies are usually discontinued as they require functioning beta cells in order to be effective. If there is significant insulin resistance, a TZD may be maintained, but with caution due to the increased risk of fluid retention if these are given together with insulin. (Note: TZD + insulin is not an approved indication in Canada.)

Calculating basal and bolus insulin needs

Usual total insulin dose is about 0.5 to 2 unit/kg of body weight divided into 40% basal and 60% bolus insulin. The bolus insulin dose is dynamic and changes with carbohydrate intake ± a high glucose correction according to premeal glycemia.

A typical bolus dose would be 1 unit for each 10 to 15 g of carbohydrate in the meal, +1 unit if pre-meal glucose is >8.0 mmol/L, +2 units if >10.0 mmol/L, +3 units if >12.0 mmol/L etc. This regimen rapidly lowers postprandial glucose levels and reduces total insulin dose to the minimal effective and required dose. There is no excess insulin to stimulate appetite and weight gain, there is also less risk of hypoglycemia as bolus insulin is given only with meals, and the action of the insulin closely parallels the glycemic response to the food.

If an adequate carbohydrate-to-insulin match is established (i.e. two-hour postprandial glucose levels are normal), but the glucose level consistently rises from the two-hour postprandial level to the next pre-meal level, the patient is not producing sufficient basal insulin and will need an increase in basal (long-acting) insulin.

Patients on intensive insulin therapy should see a dietitian to learn carbohydrate counting in order to match insulin dose to actual food intake and should keep detailed monitoring records in their diary.

INJECTION DEVICES

Insulin pens

- Insulin pens are the simplest injection devices. Starting insulin with syringes adds another level of complexity of treatment to a patient who is already facing enough challenges.

- Reusable pens accept a 3-cc insulin cartridge.
- A unique pen is required for each brand of insulin.
- **Do not** use the pen of one manufacturer with the cartridge of another.
- Pens are generally provided free by the manufacturer; the costs of the cartridge or disposable pen are equivalent.

Getting started with a pen

In my practice, I supply the patient with the first cartridge and recommend a fixed insulin dose until the first follow-up visit. The cartridge of insulin that is in use and the pen do not need to be refrigerated. Get the patient to put the cartridge in the pen and attach the needle under supervision. One should always try to observe the patient giving the first insulin injection so that any potential problems can be noted and dealt with. In the office, a reduced dose of 2 or 3 units may be given to observe the technique. Alternatively the patient can be referred to a diabetes education centre or pharmacy for insulin instruction.

I usually start with a dose of 10 units of insulin at bedtime and instruct patients to bring the pen back at the first follow-up visit in 28 to 30 days. A quick glance at the cartridge will tell us whether we have an adherence problem, since there should be only enough insulin left for one or two injections. When we have determined that the patient is comfortable and compliant with taking the insulin, we can deal with changing cartridges, storage of extra cartridges, dosage titration etc.

Changing pen needles

Needles should be changed each time an injection is given. They are Teflon coated and almost totally painless. However, the Teflon coating wears off after the first use and injections become progressively more painful. At least for the first month, the needle should be changed each time, so the patient doesn't dread the injection. People with diabetes frequently re-use needles. The incidence of infection is very low, but being single-use devices, reuse can't ethically be suggested. Needles must be changed when cartridges are changed. Alcohol swabs are not needed.

Coverage by provincial plans and formularies

Insulin pens are available through the insulin companies free of charge and may be obtained at diabetes education centres or pharmacies.

Patient information

The Canadian Diabetes Association, as well as insulin companies, have produced educational material (pamphlets, and videos) on pens and insulin administration. It is important to allow the patient time to become comfortable with the injection, monitoring, and needle and cartridge changing.

HUMULIN or HUMALOG (by Eli Lilly)

Humapen Luxura (champagne or burgundy): Takes a 3-cc Lilly cartridge. Dose adjusts in 1-unit increments to maximum dose of 60 units.

Humapen Luxura HD (champagne, green or burgundy): Takes a 3-cc Lilly cartridge. Dose adjusts in ½-unit increments to maximum dose of 60 units.

Humapen Memoire (burgundy): Takes a 3-cc cartridge. Dose adjusts in 1-unit increments, to maximum dose of 60 units. Memory records the date, time and amount of the last 16 doses.

Humalog KwikPen (blue): Disposable 3-cc (300 unit) pen. Dose adjusts in 1-unit increments up to maximum dose of 60 units. Available with Humalog, Humalog Mix-25 and Humalog Mix 50.

NOVOLIN GE, NOVOMIX, NOVORAPID, LEVEMIR

(by NovoNordisk)

Novolin Pen 4 (silver or blue): Takes a 3-cc Novo Nordisk cartridge. Dose adjusts in 1-unit increments to maximum dose of 60 units.

Novolin Pen Junior (blue with green or yellow with green): Takes a 3-cc NovNordisk cartridgeDose adjusts in ½-unit increments to maximum dose of 35 units.

Novopen Echo (red or blue): Takes a 3-cc NovoNordisk cartridge. Dose adjusts in 1-unit increments to maximum dose of 60 units This pen has a memory that will display the last dose given on an LCD screen as well as the number of hours (in 1-hour increments up to 12 hours since the last dose was given).

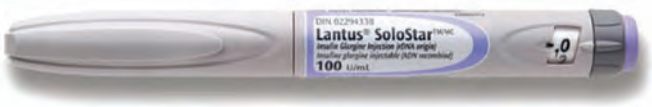
Novolin Levemir Flexpen:
Disposable 3-cc (300-unit) pen. Dose adjusts in 1-unit adjustments up to maximum of 60 units. Available with NovoRapid, NovoMix 30 or Levemir.

LANTUS, APIDRA (by sanofi-aventis)

ClikSTAR Pen (grey or blue): Takes a 3-cc Lantus or Apidra cartridge. Dose adjusts in 1-unit increments to maximum dose of 80 units.

AutoPen 24 (blue or green): Takes 3-cc Lantus or Apidra cartridge. Dose adjusts in 1-unit increments to maximum dose of 42 units (blue) or in ½-unit increments to maximum dose of 21 units (green). This pen is being replaced by the ClikSTAR and will be phased out by 2012.

SoloSTAR Pen: Disposable 3-cc (300-unit) pen for use with either Lantus (grey) or Apidra (blue). Dose adjusts in 1-unit increments to a maximum dose of 80 units.



TREATMENT – HYPOGLYCEMIA

Patients must learn to how to prevent, recognize and treat hypoglycemia. If patients suspect hypoglycemia, they should always confirm it with capillary glucose testing, and record the results in their diary.

Hypoglycemia

Hypoglycemia is defined by:

1. autonomic or neuroglycopenic symptoms;
2. plasma glucose <4.0 mmol/L; and
3. symptoms responding to the administration of carbohydrate.

The severity of hypoglycemia is defined by clinical manifestations (see Table 11):
Mild: autonomic symptoms are present and patient can self-treat
Moderate: autonomic and neuroglycopenic symptoms are present and spatient can self-treat
Severe: patient may be unconscious or require assistance (PG is typically <2.8 mmol/L)

Table 11. Symptoms of hypoglycemia

Autonomic	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
Tingling	Headache
	Dizziness

» **The most common symptoms of hypoglycemia are sweating, hunger and trembling.** «

- Ask about hypoglycemia at every visit.
- All patients on insulin or insulin secretagogues should be counseled about the risk factors for hypoglycemia, and the recognition, prevention and treatment of drug-induced hypoglycemia. Since hypoglycemia unawareness may develop with increased frequency of hypoglycemia, the frequency of such episodes should be minimized (fewer than three episodes/week). One should always consider the cause of the hypoglycemia. For example, the risk of recurrent hypoglycemia may remain until the peak action of an intermediate- or long-acting insulin has passed.
- If A1C ≤7.0% cannot be achieved without frequent hypoglycemia, refer to a diabetes specialist.

Treatment of hypoglycemia

- The preferred carbohydrate for treatment of hypoglycemia is glucose or sucrose tablets or solution, rather than orange juice or glucose gel.
- **Mild** or **moderate** hypoglycemia should be treated by oral ingestion of 15 g of carbohydrate.
- **Severe** hypoglycemia in a conscious adult who is able to swallow should be treated by oral ingestion of 20 g of carbohydrate.
- Patients should wait 15 minutes and retest blood glucose. If glucose remains <4.0 mmol/L, treat again with another 15 g of carbohydrate. Continue this cycle until glucose is in the normal range.

CAUTION:
Do not overtreat hypoglycemia

Glucagon treatment

Severe hypoglycemia with unconsciousness or inability to take oral carbohydrate should be treated with 1 mg 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. Since the person with severe hypoglycemia is unable to self-treat, it is very important to train the spouse, a family member or support person to administer glucagon.

Patients on **MDI** or **insulin pumps** should have glucagon available for administration by a support person if they are unconscious or unable to take oral carbohydrate. Support persons at home or at work should be taught when and how to administer glucagon by injection (for further details, visit www.diabetesclinic.ca).

Capillary glucose monitoring should be done 15 minutes after glucagon injection and the recommendations above for moderate hypoglycemia should be followed to prevent repeated hypoglycemia. Once the hypoglycemic episode has been treated, the person should have their usual meal. A snack including 15 g carbohydrate and a protein source should be taken if a meal is more than one hour away.

Remember:
Prevention of hypoglycemia is the best treatment.

Overnight hypoglycemia with high blood glucose levels in the morning
If you see increasing fasting levels despite increases in bedtime insulin, the patient may be having undetected hypoglycemic reactions during the night (Somogyi effect). To confirm, have the patient set an alarm clock for 3:00 AM for a few nights and instruct them to check the capillary glucose level (and record in the diary). If the value is low (<4.0 mmol/L), the bedtime insulin dose should be reduced or the patient should be switched to long-acting insulin analogue such as glargine (Lantus) or detemir (Levemir). Overnight hypoglycemia is usually caused by NPH insulin and is less common when these long-acting analogues are used.

SCREENING, MONITORING & MANAGEMENT OF COMPLICATIONS & CO-MORBIDITIES

An integral part of the management of diabetes is the timely and appropriate screening and management of the macro- and microvascular complications of the disease. Screening for all complications should commence at the diagnosis of diabetes, and occur at the intervals indicated in Table 12.

Lifestyle counts! It is important to do a quick assessment of what your patients eat and drink, and how much exercise they do. A more detailed assessment of dietary practices and meal plans should be provided by a registered dietitian. ***Remember:*** patients are more likely to change their habits if the doctor says they should!

Table 12. Screening and monitoring of complications and co-morbidities

Complication	*Screening test*	*Follow-up/screening intervals*
Coronary artery disease	Assessment of risk factors and ECG	Risk factor assessment: periodically Resting ECG: baseline ECG, then every two years if >40 years, duration of diabetes, symptoms etc.
Dyslipidemia	Full lipid profile: TC to HDL-C ratio, TG, and calculated LDL-C	Every one to three years as clinically indicated. More frequently if treatment for dyslipidemia is started.
Hypertension	BP measurement	At every diabetes-related visit
Chronic kidney disease (CKD)	Random urine ACR and serum creatinine converted to an eGFR	Annually if no CKD. At least twice a year if CKD present.
Neuropathy	Loss of sensitivity to a 10-g monofilament or vibration at the great toe	Annually.
Foot problems	Foot examination	Annually. More often in those at high risk.
Retinopathy	Dilated eye exam by experienced eye care professional	Every one to two years (depending on whether retinopathy is present).
Erectile dysfunction	Sexual function history	Periodically.
Depression	Interview or standardized questionnaire	Periodically.

Vascular protection

Diabetes is a cardiovascular disease.[29] People with type 2 diabetes have a high incidence (up to 75%) of hypertension and dyslipidemia. In addition, microalbuminuria is an independent risk factor for CV events. Aggressive management of risk factors is therefore recommended to reduce morbidity and mortality due to vascular events. In the STENO-2 Trial[7] an intensive multifactorial approach to risk factor management in high-risk patients reduced CVD and microvascular events by over 50%.

The first priority in the prevention of diabetes complications should be reduction of CV risk by vascular protection through a comprehensive multifaceted approach including: lifestyle modification (diet and exercise and smoking cessation), BP, lipid and glycemic control; renin/angiotensin (ACE/ARB) therapy (as indicated); statin therapy (as indicated) and antiplatelet therapy (as indicated).

Hypertension

Goal: ≤130/80 mm Hg

Treatment: Start with an ACE inhibitor or ARB. Titrate to full therapeutic dose, then add other agents (cardioselective beta blocker, low-dose thiazide-like diuretic, long-acting calcium channel blocker, direct renin inhibitor) until goal has been reached. Concurrent treatment with ACE inhibitors and certain NSAIDs (e.g. ibuprofen) carries a risk of inducing renal failure.[30]

While concurrent treatment with ACE/ARB for hypertension is not indicated, the combination may be useful in decreasing proteinuria in persons with nephropathy.

Dyslipidemia

Goals:

Primary target:

LDL-C: ≤2.0 mmol/L*[1], (or to decrease LDL-C by 50%)[31]

*Use clinical judgment to decide if additional LDL-C lowering is needed in patients with an on-treatment LDL-C of 2.0 to 2.5 mmol/L. High-sensitivity C reactive protein levels (hs-CRP) may help to quantify risk.[31]

Secondary target:
TC/HDL-C ratio: <4.0

Treatment:

- **LDL above target**: lifestyle + statin
- **TC/HDL-C above target**: improved glycemic control, intensification of lifestyle modifications, and if needed, pharmacotherapy
- **TG of 4.5 to 10.0 mmol/L**: either statin or fibrate as first-line therapy. If target not achieved after four to six months of monotherapy, add another lipid-lowering agent from different class. Encourage the following lifestyle changes: weight loss, physical activity, smoking cessation, restriction of refined carbohydrates and alcohol.
- **TG >10.0 mmol/L** despite best efforts at glycemic control and lifestyle: fibrate (to reduce risk of pancreatitis)

When optimally dosed first-line therapy fails to achieve lipid targets, consider adding a second drug from another class (e.g. statin + ezetimibe, or statin + fibrate, or statin + niacin).

Antiplatelet therapy

- Patient with diabetes have a variety of alterations in platelet function that put them at risk for thrombosis and increased platelet activation.
- Antiplatelet therapy, however, may confer less benefit for CV event reduction in those people with diabetes compared with those without diabetes.
- Low-dose ASA therapy may be considered in people with stable CVD.
- The decision to prescribe ASA for primary prevention of CVD should be based on clinical judgment.
- Low-dose ASA, the most widely studied agent, is as effective as other antiplatelet agents and is the most economical. Treat with ASA 81 to 325 mg, if tolerated.
- If ASA-intolerant, consider clopidrogrel (Plavix) 75 mg.

ADHERENCE TO MEDICATION REGIMENS

In the UKPDS,[18] 75% of subjects needed multiple medications to control hyperglycemia. In the Hypertension Optimal Treatment trial[32] subjects needed an average of 3.5 different prescriptions. In addition to antihyperglycemics, we generally, prescribe a statin, and an ACE inhibitor or an ARB almost every patient with diabetes. As such, many patients require eight or nine prescriptions just for diabetes and its related comorbidities. Paes et al[33] showed that people prescribed one pill once a day take the pill 79% of the time; if the dose is divided to twice a day, compliance falls to 65%, and if the pill is prescribed three times a day, it is taken correctly only 38% of the time. Thus we should try to simplify medication regimens by using once-a-day dosing or combination agents when appropriate.

» Simplify medication regimens whenever possible to enhance adherence. «

- Educate patients and families on the consequences of diabetes and the benefits of lifestyle and drug therapy.
- Involve patients in tailoring drug regimens to fit their daily habits (same time/place/situation).
- Give pills once a day if possible and try to avoid more than twice a day.
- Use combination products to reduce the number of pills and dispensing costs wherever possible. Use extended-action products.
- Discuss barriers to adherence with patients. For example, is one time of the day more convenient than another? Could the use of a medication dispenser such as a dosette help?
- Generally, 75 to 85% of the maximal therapeutic effect is achieved from 50% of the maximum therapeutic dose.[34]
- Counsel patients on side effects and how to avoid or minimize them.
- Discuss cost issues with the patient to ensure the regimen is affordable.

- It is often less expensive to give half a tablet of a higher dose or to use alternate-day therapy with products like statins.
- Sometimes, we clinicians must make compromises regarding pharmacotherapies, such as using less expensive alternatives or generics.
- Stress that sustained lifestyle changes sometimes allow patients to reduce the number and/or dosages of certain medications.
- Encourage patient responsibility/autonomy in monitoring blood glucose and adjusting prescriptions.
- Maintain regular follow-up.

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GLOSSARY OF ACRONYMS

2hPG	2-hour plasma glucose
A1C	glycated hemoglobin
ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
ASA	acetylsalicylic acid
BP	blood pressure
DKA	diabetic ketoacidosis
CAD	coronary artery disease
CHF	congestive heart failure
CVD	cardiovascular disease
DICE	Diabetes in Canada Evaluation
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase-4
eAG	estimated average glucose
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
GI	gastrointestinal
GIP	glucose-dependant insulinotropic peptide
GLP-1	glucagon-like peptide-1
HDL-C	high-density lipoprotein cholesterol
hs-CRP	high-sensitivity C reactive protein
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
K-ATP channel	ATP-sensitive potassium channel
LDL-C	low-density lipoprotein cholesterol
MDI	multiple daily injections
NSAID	nonsteroidal anti-inflammatory drug
OGTT	oral glucose tolerance test
PG	plasma glucose
PPAR	peroxisome proliferator-activated receptor
SMBG	self-monitoring of blood glucose
TC	total cholesterol
TG	triglycerides
UKPDS	United Kingdom Prospective Diabetes Study

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