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 sequelae, 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 about 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, 1 out of every 5 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 as the “baby boomers” age. The Canadian Diabetes Association (CDA) suggests that by the year 2010, 1 in 4 Canadians over the age of 45 will have type 2 diabetes. The lowering of the diagnostic criteria (in 1998) means that diabetes is being recognized in more people at an earlier age\(^4\). The annual cost to the Canadian healthcare system is currently estimated at over $13 billion\(^5\). The incidence and related costs will continue to increase unless effective prevention strategies can be implemented.

In Canada, 95% of type 2 diabetes patients are treated by a family physician, whereas 80% of type 1 patients are followed by an endocrinologist or diabetes treatment centre\(^6\). Thus, as family physicians, we need to develop the expertise to function as a key member of the multidisciplinary treatment 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% [8]. Improving the quality of life for our patients with diabetes will require multifactorial 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 the most current approaches to screening, monitoring and treatment of diabetes and its related complications.

**Diabetes**
Type 2 diabetes mellitus 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 level. Insulin resistance is a decrease in insulin sensitivity.

**Natural history 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.

**Prediabetes**
For impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), we now use the term prediabetes, as it identifies those individuals at high risk for development of diabetes and cardiovascular disease (CVD). The vast majority of these patients will also have the metabolic syndrome. The aim in treating prediabetes is to prevent conversion to diabetes. 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% [9-10]. In individuals with IGT, new-onset diabetes can be reduced by 30% with metformin (Glucophage) [9], and by 25% with acarbose (Prandase) [11]. The potential of thiazolidinediones in diabetes prevention is currently being investigated in the DREAM trial (using rosiglitazone [Avandia]).

**Metabolic syndrome**
A clustering of certain features, including central obesity, hypertension, dyslipidemia and dysglycemia, is commonly known as the “metabolic syndrome.” Metabolic syndrome is very common, with almost 45% of the US population over age 50 meeting the criteria listed on page 4 [12]. It is estimated that approximately 87% of people with type 2 diabetes also have the metabolic syndrome [13]. The prevalence of coronary heart disease (CHD) increases significantly with the metabolic syndrome. Those with metabolic syndrome but without diabetes have a CHD prevalence of 14%. Individuals with the metabolic syndrome and diabetes have a CHD prevalence of 19% [14].

Those with metabolic syndrome are at very high risk of developing type 2 diabetes. The metabolic syndrome is also associated with increased CVD risks that are almost identical to type 2 diabetes [15].

As risk factors tend to be associated, patients with 1 feature of the metabolic syndrome should be screened for each of the other feature. (See Diagnosis on p. 4 and Screening, Monitoring and Management of Complications on p. 35). Cardiovascular 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 changes 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 may increase HDL-C and lower triglycerides and blood pressure (BP).
Clinical identification of the metabolic syndrome using NCEP ATP III criteria

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>≥ 6.1 mmol/L</td>
</tr>
<tr>
<td>BP</td>
<td>≥ 130/85 mm Hg</td>
</tr>
<tr>
<td>TG</td>
<td>≥ 1.7 mmol/L</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 1.0 mmol/L</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 1.3 mmol/L</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>Men</td>
<td>&gt; 102 cm (&gt; 40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt; 88 cm (&gt; 36 in)</td>
</tr>
</tbody>
</table>

* A diagnosis of metabolic syndrome is made when 3 or more of the risk determinants are present.

Glucose levels for diagnosis of prediabetes and diabetes

<table>
<thead>
<tr>
<th></th>
<th>FPG (mmol/L)</th>
<th>2hPG in a 75-g OGTT (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired fasting glucose (IFG)</td>
<td>6.1 – 6.9</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Impaired glucose tolerance (IGT)</td>
<td>&lt; 6.1</td>
<td>and 7.8 – 11.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥ 7.0</td>
<td>or ≥ 11.1</td>
</tr>
</tbody>
</table>

Testing with a 2hPG in a 75-g OGTT should be considered in individuals with an FPG of 5.7 to 6.9 mmol/L plus risk factors in order to identify individuals with IGT or diabetes.

Diagnosis of Diabetes

- A fasting plasma glucose (FPG) ≥ 7.0 mmol/L
  - OR
  - Symptoms of diabetes plus a casual PG value ≥ 11.1 mmol/L
  - OR
- A PG value in the 2-h sample (2hPG) of the 75-g oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L

A confirmatory laboratory test must be done on another day in all cases in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation.
DIABETES KNOWLEDGE CHECKLIST

Test your knowledge of what’s new in diabetes treatment.

Check the box if you are aware of the following:

☐ In individuals with IGT, a structured program of lifestyle modification that includes modest weight loss and regular physical activity should be implemented to reduce risk of type 2 diabetes. Pharmacologic therapy with 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/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 ≤ 6.0% or less if safely achievable).

☐ The first priority in the prevention of diabetes-related complications is the reduction of CV risk.

☐ BP target for all people with diabetes is ≤ 130/80 mm Hg.

☐ ACE inhibitor therapy, as part of a multifaceted approach to vascular protection, is often indicated for people with diabetes. This is particularly important in patients with increased vascular risk, such as those with hypertension or elevated microalbuminuria.

☐ Vascular protection should also include ASA therapy (as indicated), BP, glycemic and lipid control, lifestyle modifications and smoking cessation.

☐ Guideline-recommended lipid targets for most people with diabetes are LDL-C < 2.5 mmol/L and TC/HDL-C ratio < 4. A statin is indicated if LDL-C is above target. Recent evidence supports lowering the target to < 2.0 mmol/L.

☐ 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.

THE DIAGNOSIS OF TYPE 2 DIABETES IS MADE, NOW WHAT?

Organization of 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. A sample flow sheet is included in the inside back cover. Other flow sheets are available, including one that can be downloaded from the Canadian Diabetes Association guideline website (http://www.diabetes.ca/cpg2003/downloads/appendix3.pdf).

Lifestyle education

- 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 generally incorporating diabetes self-care practices into their activities of daily living.
- Encouragement and strategies for 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 it from www.mealsforgoodhealth.com or 1-866-733-9409.
Screening for complications
Screening for early complications is indicated at the time of diagnosis of diabetes since one-third of those newly diagnosed will have some form of complication.

- Blood glucose
- Blood pressure
- Lipid profile
- Dilated eye exam
- Thorough foot exam, including screening for peripheral neuropathy
- Screening for microalbuminuria
- Sexual function history

Follow-up
A follow-up appointment should be made to assess management goals and to adjust therapy as needed. One of the reasons patients sometimes fail to achieve treatment targets is that we, as their healthcare professionals, fail to follow up regularly and adjust their treatments as needed. Our patients with diabetes should never leave our offices without booking a follow-up appointment. In the stable patient who is meeting treatment targets, we should follow up and do an A1C approximately every 3 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.

GLYCEMIC TARGETS
The 2003 Canadian Diabetes Association’s Clinical Practice Guidelines recommend the following targets. Therapy in most patients with diabetes should be tailored to achieve an A1C \( \leq 7.0\% \) in order to reduce the risk of microvascular and macrovascular complications. Lowering glycemic levels toward the normal range (i.e. \( \leq 6.0\% \)) should be considered for patients in whom it can be achieved safely.

<table>
<thead>
<tr>
<th>Recommended glycemic targets (^{(1)})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting/preprandial</strong></td>
</tr>
<tr>
<td>Normal*</td>
</tr>
<tr>
<td>Target</td>
</tr>
<tr>
<td><strong>2 hours postprandial</strong></td>
</tr>
<tr>
<td>Normal*</td>
</tr>
<tr>
<td>Target</td>
</tr>
<tr>
<td><strong>A1C</strong></td>
</tr>
<tr>
<td>Normal*</td>
</tr>
<tr>
<td>Target</td>
</tr>
</tbody>
</table>

* The normal range should be considered if it can be safely achieved.
CHOOSING A TREATMENT REGIMEN

Lifestyle
All patients with diabetes should receive healthy lifestyle counselling. While lifestyle remains a cornerstone of diabetes treatment, many patients find it difficult to maintain the necessary changes over the long term. For this reason, the CDA guidelines recommend that physicians not rely on lifestyle alone for too long.
- 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 Canada’s Guidelines for Healthy Eating.
- 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 or, if willing, 4 hours or more of exercise per week.
- Patients should be encouraged to perform resistance exercise 3 times per week.
- An exercise 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.

Pharmacotherapy
If glycemic targets have not been met within 2 to 3 months on lifestyle management alone, antihyperglycemic agents (oral agents and/or insulin) should be initiated. If marked hyperglycemia (i.e. A1C ≥ 9.0%) is present at diagnosis, pharmacotherapy should be initiated immediately (concomitant with lifestyle counselling).

Most oral agents have the potential to lower A1C by about 1.0 to 1.5% (acarbose [Prandase], nateglinide [Starlix], and orlistat [Xenical] lower A1C by about 0.5%). Thus, if initial A1C is ≥ 9.0%, initial combination therapy should be considered targeting insulin resistance and insulin sensitivity.

The UKPDS demonstrated that 2, if not 3, different agents in combination will frequently be required. If glycemic targets are not met on monotherapy, agent(s) from another class should be added. Adding a drug from another class of agents often addresses the progressive nature of hyperglycemia. The initial use of combinations of submaximal doses, compared to 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. Combined formulations are available for rosiglitazone + metformin (Avandamet), and rosiglitazone + glimepiride (Avandaryl). Do not combine drugs in the same class, such as a sulphonylurea with a meglitinide. Where metabolic decompensation is present, initial use of insulin should be considered (see Insulin, p. 19).

There are many factors to consider when choosing a pharmacologic treatment regimen, including:
- Level of glycemia and presence of symptoms of diabetes
- Age of the patient
- Predominance of insulin resistance or insulin deficiency
- Renal and hepatic function
- Cardiovascular disease
- 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
Management of hyperglycemia
The following algorithm summarizes the guideline-recommended approach to the management of hyperglycemia in type 2 diabetes.

Lifestyle
Initiate lifestyle modifications. 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 2 or 3 months. If A1C ≥ 9.0%, consider initial pharmacologic therapy.

Pharmacotherapy in addition to lifestyle
If A1C < 9.0%, treatment will depend on body mass index (BMI):
- If overweight (BMI ≥ 25 kg/m²), initiate therapy with metformin alone or in combination with 1 of following drugs (in this order): thiazolidinedione (TZD), secretagogue, insulin, acarbose.
- If not overweight (BMI < 25 kg/m²), initiate therapy with 1 or 2 of the following drugs (in this order): metformin, TZD, secretagogue, insulin, acarbose. If patient does not achieve target A1C, add a drug from a different class or use insulin in combination with oral agents (see precautions re: use of TZD plus insulin, p.13).

If A1C ≥ 9.0%:
1) Initiate combination therapy with 2 agents from different classes (see above). If patient does not achieve target, add another oral agent (i.e. a third agent) from another class or add insulin.

OR
2) Initiate basal and/or preprandial insulin. If patient does not achieve target, intensify the insulin regimen or add an oral agent (in this order): metformin, secretagogue, TZD, acarbose. (See precautions re: use of TZD plus insulin). The lag period between adding antihyperglycemic agents should be kept to minimum, with consideration given to the pharmacokinetics of the agents used. Metformin and sulphonylureas reach maximum effect very rapidly, but the TZDs (glitazones) may take several months to show maximal effect.

Timely adjustments to and/or additions of oral antihyperglycemic agents and/or insulin should be made to attain target A1C within 6 to 12 months.
Agents are listed in order of preference (Consensus of the 2003 CDA guideline committee).
Adapted with permission from: Can J Diabetes. 2003;27(Suppl 2):S39

* When used in combination with insulin, insulin sensitizers may increase the risk of edema or CHF. The combination of an insulin sensitizer and insulin is currently not an approved indication in Canada.
** If using preprandial insulin, do not add an insulin secretagogue.
† May be given as a combined formulation: rosiglitazone plus metformin (Avandamet) or rosiglitazone plus glimepiride (Avandaryl).
TREATMENT - ORAL AGENTS

BIGUANIDE

Acts mainly by reducing hepatic glucose production. 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). Can cause gastric discomfort and diarrhea, and has been associated with lactic acidosis in the presence of renal or hepatic dysfunction. Taken with meals in order to decrease gastric irritation. Not associated with weight gain and works particularly well with a TZD. Does not cause hypoglycemia. May be used with insulin.

Metformin (Glucophage)

- **Tablets**: 500 mg and 850 mg
- **Starting dose**: ½ a 500-mg tablet daily
- **Titration/dosing**: Titrated to a maximum dose of 2.5 g/day. Very little additional benefit at doses > 1500 mg/day.

Slow-release metformin (Glumetza)

- **Tablets**: 500 mg
- **Starting dose**: 1000 mg OD
- **Titration/dosing**: Titrated to a maximum dose of 2 g OD (4 x 500 mg OD). Recommended once daily with the evening meal. Very little additional benefit at doses > 2000 mg/day.

THIAZOLIDINEDIONES (TZDs OR GLITAZONES)

Increase insulin sensitivity and decrease hepatic glucose production. TZD monotherapy is not currently indicated in the symptomatic patient in Canada; rather, a combination with metformin or a secretagogue or insulin to reduce glucose toxicity may be needed initially until therapeutic levels of TZD are reached. 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. Do not use in patients with CHF (NYHA Class III or 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. Liver function tests should be done before therapy to rule out active liver disease. Not recommended in patients with active liver disease. Only if symptoms warrant should follow-up liver function tests be performed.

Rosiglitazone (Avandia)

- **Tablets**: 2 mg, 4 mg, 8 mg
- **Starting dose**: Usual starting dose 4 mg OD
- **Titration/dosing**: 8 mg in 3 months if glycemic goals have not been reached. Dosage range is 2 mg to 8 mg/day; 4 mg BID is most effective.

Pioglitazone (Actos)

- **Tablets**: 15 mg, 30 mg, 45 mg
- **Starting dose**: Usual starting dose 30 mg
- **Titration/dosing**: Increase to 45 mg in 3 months if needed. Dosage range is 15 to 45 mg.

INSULIN SECRETAGOGUES

Long-acting (sulphonylureas) and short-acting (meglitinides)

Sulphonylureas

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

Glyburide (DiaBeta, Euglucon)

Non-selective and increases insulin output regardless of glucose levels, thus it may cause severe and prolonged hypoglycemia, especially in the elderly.

- **Tablets**: 2.5 mg, 5 mg
- **Starting dose**: 2.5 mg OD
- **Titration/dosing**: Maximum dose is 10 mg BID. Dosage range is 1.25 to 20 mg/day. Usual dose is 5 to 10 mg BID. Doses 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. Restores first-phase insulin release secretion. No dose adjustment needed in the elderly or those with mild to moderate renal failure (creatinine clearance 15 to 80 mL/min).

*Diamicron*
- **Tablets**: 80 mg
- **Starting dose**: 40 to 80 mg BID
- **Titration/dosing**: Dosage range 40 to 360 mg/day, given in divided dose BID

*Diamicron MR*
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 dose**: 30 mg OD in the morning
- **Titration/dosing**: Dosage range 30 to 120 mg daily. Titrate to maximum of 120 mg (i.e. 1 – 4 tablets) as 1 dose/day.

**Glimepiride (Amaryl)**
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 dose**: 1 mg OD
- **Titration/dosing**: Dosage range 0.5 to 8 mg/day

**Meglitinides (GlucoNorm, Starlix)**
Very short-acting insulin secretagogues, taken with meals. Cause less hypoglycemia than sulphonylureas 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 dose**: 0.5 mg taken with meals
- **Titration/dosing**: Dosage range 0.5 to 4 mg before each meal

**Nateglinide (Starlix)**
Insulin release is glucose dependant.
- **Tablets**: 120 mg
- **Starting dose**: 120 mg
- **Titration/dosing**: 120 mg with each meal

**ALPHA-GLUCOSIDASE INHIBITOR**
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.

**Acarbose (Prandase)**
High incidence of GI side effects (flatulence and diarrhea), which can be lessened if titrated slowly. 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.
- **Tablets**: 50 mg, 100 mg
- **Starting dose**: 25 mg with the first bite of each meal
- **Titration/dosing**: Dose 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-OBESEITY AGENT**

**Orlistat (Xenical)**
Approved for the treatment of type 2 diabetes accompanied by obesity. May be used as an adjunct in the obese. Decreases fat absorption. 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%.

*Tables:* 120 mg

*Starting dose:* One tablet with the largest meal of the day

*Titration/dosing:* Increase to 1 tablet with each meal

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**COMBINED ORAL AGENT FORMULATIONS**

There are some agents currently available on the market that incorporate 2 agents into 1 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 also Adherence to Medication Regimens, p. 38) and since a fixed combination may incur only 1 dispensing fee, there may be cost savings. The only currently available combinations in Canada are:

**Avandamet (Avandia [rosiglitazone] plus metformin)**
Available in 1/500, 2/500 2/1000, 4/500, 2/1000 and 4/1000 mg dose tablets

**Avandaryl (Avandia [rosiglitazone] plus Amaryl [glimepiride])**
Available in 4/1, 4/2 and 4/4 mg dose tablets

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**TREATMENT - INSULIN**

**INSULIN**
Initial use of insulin can be considered in the patient with marked hyperglycemia (A1C ≥ 9.0%) or metabolic decompensation at diagnosis. Many physicians and patients alike resist the initiation of insulin. It is important to overcome this barrier. Patients who are not initially motivated should be encouraged to try insulin. 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 patients) can do very well on insulin administered by someone else.

If adequate control (A1C ≤ 7.0%) cannot be maintained on oral agents alone, we should add bedtime insulin, using an intermediate-acting insulin (NPH [Humulin or Novolin]), or an extended long-acting insulin analogue (glargine [Lantus] or detemir [Levemir]). Patients who have had diabetes for > 10 years often need addition of bedtime insulin.

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

**Adding bedtime insulin to daytime oral agents**
When lifestyle modifications and oral agents are no longer able to maintain an A1C in the target range (A1C ≤ 7.0%), the addition of intermediate-acting insulin (NPH) or an extended long-acting insulin analogue (glargine [Lantus] or detemir [Levemir]) at bedtime may achieve better glucose levels in the morning, thereby decreasing glucose toxicity and allowing the daytime oral agents to be more effective. Frequently in type 2 diabetes, the highest glucose value of the day is the fasting value in the morning. This is primarily caused by overnight hepatic glucose production.

The dawn phenomenon, characterized by increased steroid levels (particularly growth hormone levels), 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 yield a lower fasting glucose. 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.
Advantages of bedtime insulin
Bedtime 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 1 injection/day
- Only small doses of insulin are needed, causing less weight gain
- Can be given by insulin pen (virtually painless, no mixing needed)

Bedtime insulin options
- Extended long-acting basal insulin analogues (insulin glargine [Lantus] or insulin detemir [Levemir]). These insulins have a virtually flat profile of action over 24 hours. Because of their delayed absorption, the injection may be given at any time of the day. It may be given whenever the oral medications are taken once a day in order to enhance adherence or to increase flexibility for other healthcare providers such as home-care nurses. Insulin glargine is available in a vial or pen fill using a proprietary pen. Levemir is supplied in cartridges that fit in the Novolin pen.
- Intermediate-acting insulin (Humulin-N, Novolin ge NPH).

General principles of bedtime insulin adjustment
Since hyperinsulinemia is associated with weight gain and increases risk of hypoglycemia, we want to use the smallest possible dose of insulin to achieve our objective. We get a bigger bang for our buck by 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

**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.

**Self-monitoring:** Patient should monitor bedtime and fasting blood glucose daily (preferably before each meal and bedtime).

**Titration:** Increase the dose by 1 or 2 units after 3 successive days of a fasting blood glucose > 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 hypoglycemic symptoms with glucose levels in the normal range (< 5.0 or 6.0 mmol/L).

**Take your time.** 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 lower glucose levels and over time will develop tolerance for levels that previously made them feel hypoglycemic.

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

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

**If the patient has normal** fasting values, but develops daytime hypoglycemia, reduce the sulphonylurea or the meglitinide. 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, is willing and is monitoring well, give them instructions on how to self-adjust their insulin dose according to self-monitored fasting blood glucose levels (see sample patient instructions on p. 24). 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 3 months, referral to a diabetes clinic or endocrinologist 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. Some patients do need large doses, but beware of overnight hypoglycemia with high blood glucose levels in the morning (see p. 23).

**Hypoglycemia**

Make sure that the patient is aware of the symptoms of hypoglycemia and how to treat it. The CDA and several pharmaceutical companies have charts describing hypoglycemic symptoms. If patients suspect hypoglycemia, they should always confirm it with capillary testing, and record the results in their diary. (See page 32 for treatment of hypoglycemia.)

**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.

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 an extended long-acting insulin such as glargine (Lantus) or detemir (Levemir).
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 glucose diary), 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 3 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 3 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.
- **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 **2 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 website (www.diabetesclinic.ca) or call me at: ______________________
For emergencies outside office hours, call: ______________________

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**TREATMENT - INSULIN**

**Adding daytime insulin to oral agents**

If, despite achieving a normal fasting glucose, there is consistent hypoglycemia at certain times of the day, we can alter our insulin therapy to correct these hyperglycemic periods.

An alternative to NPH is an extended long-acting insulin (glargine [Lantus] or detemir [Levemir]). Both have a virtually flat profile of action over 24 hours and are associated with less hypoglycemia.

**Premixed insulins**

Some physicians have a comfort level with premixed insulins. These insulins are usually used twice daily. For example, a 30/70 mixture is given as 2/3 of the total daily dose in the morning and 1/3 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 2 or 3 days in a row).

Premixed insulins include the following:

- Humulin or Novolin ge 30/70 (30% regular and 70% NPH);
- Humalog Mx25 (25% rapid-acting insulin analogue [lispro] with 75% Humulin-L [NPL, an intermediate-acting insulin]);
- Novomix 30 (30% rapid-acting insulin analogue [aspart] and 70% intermediate-acting insulin analogue (neutral protamine aspart [NPA]).

A potential problem with premixed insulins given at supper time is that the intermediate-acting component (NPH, NPL or NPA) peaks about 7 or 8 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 lispro [Humalog] or insulin aspart [Novorapid]) with supper and the intermediate-acting insulin at bedtime.
However, a more logical approach is a basal/bolus method (also known as intensive management or multiple daily injections [MDI]) in which a short-acting (bolus) insulin (lispro [Humalog] or aspart [NovoRapid]) 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. This is described in more detail on pages 27 and 28.

**Adjusting oral agents**

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. Oral agents, certainly the sulphonylureas, may be discontinued at this point, as the patient is receiving exogenous insulin support. In practice, I have found that sometimes if the patient is on rosiglitazone (Avandia), pioglitazone (Actos) or metformin (Glucophage, Glumetza), continuing on these medications decreases the total dose amount of insulin required for control. We need to be cautious when giving insulin together with a TZD (glitazone), as this combination may increase the risk of fluid retention or CHF. This combination is approved in the US, but is currently not an approved indication in Canada. As this is an “off-label” use of TZDs, remember to inform the patient and note in the chart.

**Remember**

- Don’t give up until A1C is in the target range of $\leq 7.0\%$ (or $\leq 6.0\%$ if safely achievable)
- Normal fasting or preprandial glucose is 4.0 to 6.0 mmol/L.
- Talk to your patients about their diet and exercise habits and encourage improvements.

**Intensive insulin therapy**

Intensive insulin therapy requires the discontinuation of some oral agents and the initiation of multiple daily insulin injections (MDI) in order to closely mimic the healthy body’s basal and bolus insulin secretion patterns. Frequently, metformin is maintained and if there is significant insulin resistance a TZD (rosiglitazone [Avandia] or pioglitazone [Actos]) may be maintained, but with caution because of the increased risk of fluid retention. (Note: TZD + insulin is currently not an approved indication in Canada.)

**Basal insulin**

Insulin is involved in glucose transfer across cell membranes in order to provide the energy required for living. Postprandially, insulin removes glucose from the blood and stores it as glycogen and fat. 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, 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:
- An extended long-acting insulin (glargine [Lantus] or detemir [Levemir]) given once a day. With virtually constant insulin action over a 24-hour period, these insulins provide the closest to an ideal basal insulin supply. Since these insulins have no activity peak, they also cause less hypoglycemia than NPH.
- An intermediate-acting insulin (NPH) given twice a day.
Calculating minimal lowers postprandial glucose levels are normal, but the glucose level consistently rises from the 2-hour postprandial level to the next premeal level, the patient is not producing sufficient basal insulin and will need supplemental 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.

Insulin delivery devices
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. In my practice, I supply the patient with the first cartridge and recommend a fixed dose until the first follow-up visit. The insulin pen contains 3 cc (300 units) of insulin. The cartridge of insulin that is in use and the pen do not need to be refrigerated. 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. 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 a adherence problem, since there should be only enough insulin left for 1 or 2 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, 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, re-use can’t

Bolus insulin
Insulin is also 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 postprandial needs.

Postprandial hyperglycemia can be treated by giving a rapid-acting insulin analogue (lispro [Humalog] or aspart [Novorapid]) with meals. These insulin analogues have an onset of action in 10 to 15 minutes, peak in 60 to 90 minutes, and functionally wear off after 2 to 3 hours.

In an intensive insulin regimen of MDI, lispro [Humalog] or aspart [Novorapid] is given with meals in a dose to balance the carbohydrate in the meal. Dosage varies according to the amount of carbohydrate eaten.
The insulin may be taken just before the meal, with the meal, or even just after the meal. The goal is to achieve normal 2-hour postprandial values. The carbohydrate-to-insulin match can be judged by a capillary glucose measured 2 hours after the meal.

Calculating basal and bolus needs
Usual total insulin dose is about 0.5 to 2 unit/kg of body weight divided into 50% basal and 50% bolus insulin. The bolus insulin dose is dynamic and changes with carbohydrate intake ± a 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 premeal 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 hanging around all day 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. 2-hour
ethically be suggested. Needles must be changed when cartridges are
changed. Alcohol swabs are probably not needed.

Coverage by provincial plans and formularies
Insulin pens are usually available through the insulin companies free of charge
and may also be obtained at pharmacies.

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

**HYPOGLYCEMIA**

**Hypoglycemia is defined by:** 1) autonomic or neuroglycopenic symptoms;
2) a plasma glucose < 4.0 mmol/L; and 3) symptoms responding to the
administration of carbohydrate.

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

### Symptoms of hypoglycemia

<table>
<thead>
<tr>
<th>Autonomic</th>
<th>Neuroglycopenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trembling</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Confusion</td>
</tr>
<tr>
<td>Sweating</td>
<td>Weakness</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Hunger</td>
<td>Vision changes</td>
</tr>
<tr>
<td>Nausea</td>
<td>Difficulty speaking</td>
</tr>
<tr>
<td>Tingling</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
</tbody>
</table>

The most common symptoms are sweating, hunger and trembling.

- All patients on insulin or insulin secretagogues should be counselled about
  their risk factors for hypoglycemia, and the recognition, prevention and
treatment of drug-induced hypoglycemia.
- Since hypoglycemic unawareness may develop with increased frequency
  of hypoglycemia, the frequency of such episodes should be minimized
  (< 3 episodes/week).
- If A1C ≤ 7.0% cannot be achieved without frequent hypoglycemia, refer to
  a diabetes specialist.
TREATMENT - HYPOGLYCEMIA

Treatment of hypoglycemia

In adults, mild or moderate hypoglycemia should be treated by the oral ingestion of 15 g of carbohydrate, preferably as glucose or sucrose tablets or solution. Severe hypoglycemia in a conscious adult 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, retreat with another 15 g of carbohydrate. Continue this cycle until glucose is in the normal range.

CAUTION: Do Not Over-treat.

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, see 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 1 hour away.

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.

Remember PREVENTION is the best treatment.

MONITORING

MONITORING OF GLYCEMIC CONTROL

Glycated hemoglobin (A1C)

A1C should be measured approximately every 3 months to ensure that glycemic goals are being met or maintained.

| A1C goal | ≤ 7.0% (or ≤ 6.0% if achievable safely) |

Self-monitoring of blood glucose (SMBG)

All patients, who are able, should be taught how to self-manage their diabetes, including SMBG. The benefits of SMBG 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.

SMBG goals for most patients

<table>
<thead>
<tr>
<th>Before meals</th>
<th>4.0 – 7.0 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>After meals</td>
<td>5.0 – 10.0 mmol/L</td>
</tr>
</tbody>
</table>

Frequency of SMBG

The frequency of SMBG should be tailored to the patient's level of glycemic control and type of therapy. In the stable type 2 diabetes patient meeting targets, a daily capillary glucose measurement may be sufficient. For the patient on intensive management, measurements need to be made at least before each meal, as the insulin dose will be dependant on the premeal glucose level as well as the amount to be eaten. Daily testing is recommended, asking the patient to vary the time of testing, sometimes measuring fasting or before meals or sometimes testing 2 hours after meals. Both fasting as well as postmeal testing should 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 be different.
Diabetic ketoacidosis (DKA) can occur in patients with type 2 diabetes. At least annually and whenever indicators of glycemic control do not match plasma readings, a correlation between the glucose meter and laboratory screening and management of the macro- and microvascular complications of the disease. People with type 2 diabetes have high incidence (up to 75%) of hypertension and hyperlipidemia. The first priority in the prevention of diabetes complications should be reduction of CV risk by vascular protection through a comprehensive multimodal approach including ACE inhibitor therapy (as indicated), blood pressure, lipid and glycemic control, lifestyle modifications (diet and exercise), and smoking cessation. In addition, microalbuminuria is an independent risk factor for CV events.

Accuracy of SMBG

1. Ketone testing

Diabetic ketoacidosis (DKA) can occur in patients with type 2 diabetes.

2. Preprandial blood glucose levels > 140 mmol/L and

3. Symptoms of DKA (nausea, vomiting, abdominal pain).

If all the following conditions are present, patients should consider ketone testing.

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

Screening for all complications should commence at the diagnosis of diabetes and then occur at the intervals indicated in the table below.

An integral part of the management of diabetes is the timely and appropriate monitoring of the macro- and microvascular complications of the disease. People with type 2 diabetes have high incidence (up to 75%) of hypertension and hyperlipidemia. The first priority in the prevention of diabetes complications should be reduction of CV risk by vascular protection through a comprehensive multimodal approach including ACE inhibitor therapy (as indicated), blood pressure, lipid and glycemic control, lifestyle modifications (diet and exercise), and smoking cessation. In addition, microalbuminuria is an independent risk factor for CV events. Screening for all complications should commence at the diagnosis of diabetes and then occur at the intervals indicated in the table below.
Multifactorial treatment
Diabetes is a cardiovascular disease [14]. Aggressive management of risk factors is recommended to reduce morbidity and mortality due to vascular events. 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 plan should be provided by a registered dietitian. Remember: patients are more likely to change their habits if the doctor says they should!

Vascular protection
The first priority in the prevention of diabetes complications should be reduction in CV risk by vascular protection through a comprehensive multifaceted approach: ACE inhibitor and antiplatelet therapy as indicated, optimal blood pressure, lipid and glycemic control, lifestyle modifications, and smoking cessation [15].

Hypertension
Measure BP at every visit.

**Goal:** \( \text{\textless} 130/80 \text{ mm Hg} \)

**Treatment:** Start with 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) until goal has been reached. Concurrent treatment with ACE inhibitors and certain NSAIDs (e.g. ibuprofen) carries a risk of inducing renal failure [17].

Hyperlipidemia

**Goals:**
- \( \text{LDL} \text{\textless} 2.5 \text{ mmol/L} \) [Based on recent evidence [18,19], this may be lowered to \(< 2.0 \text{ mmol/L} \)]
- \( \text{TC/HDL-C ratio} \text{\textless} 4.0 \)
- \( \text{TG} \text{\textless} 1.5 \text{ mmol/L} \)

**Treatment:**
- LDL above target: lifestyle + statin
- \( \text{TG} = 1.5 – 4.5 \text{ mmol/L} \) and \( \text{HDLDL-C < 1.0 \text{ mmol/L} \) and LDL at target: lifestyle + statin or fbrate
- \( \text{TG > 4.5 \text{ mmol/L} \) lifestyle + fbrate

When monotherapy fails to achieve lipid targets, consider adding a second drug from another class.

Pro-thrombotic state
Patient with diabetes have a variety of alterations in platelet function that put them at risk for thrombosis and increased platelet activation. ASA, the most widely studied agent, is as effective as other antiplatelet agents and is the most economical. Treat with ASA 81-325 mg if tolerated. With ASA allergy consider clopidogel (Plavix) 75 mg.
ADHERENCE TO REGIMENS

In the UKPDS [15], 75% of subjects needed multiple medications to control hyperglycemia. The Hypertension Optimal Treatment [16] trial showed that treatment of hypertension needed an average of 3.5 different prescriptions. We generally recommend ASA, an ACE inhibitor and a statin to almost every patient with diabetes. Many of our patients will need 8 or 9 prescriptions just for diabetes and related comorbidities. Paes et al [17] showed that people prescribed a 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 3 times a day, it is taken correctly only 38% of the time.

Simplify medication regimen whenever possible to enhance adherence.

Educate and involve patients and families on the consequences of diabetes and the benefits of lifestyle and drug therapy.

Tailor drug regimens to fit patients’ 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 [18].

Counsel on side effects and ways to avoid/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 need to make compromises, 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.

REFERENCES


Dear Colleague,

This is the Canadian Centre for Research on Diabetes Flow Sheet designed to help primary care practitioners treat their patients with diabetes according to current Canadian Diabetes Association (CDA) guidelines.

You may use this as a stand-alone tool; but with the consent of your patient, you may also fax this sheet to us after your patient visit with all the information that you have recorded. We will enter this information into our computer, which will perform all calculations such as BMI, total cholesterol/HDL ratio and creatinine clearance. We will reprint the completed form in colour, highlighting all values that exceed CDA guideline targets in red. In addition, if there are CDA guideline recommendations that might apply to this patient, we will print them on the bottom of the form. The form will be sent back to you by mail to insert in the patient chart and use at the next visit. Once again, after the next visit, enter any medication changes or new biometric values and fax back to us. We will again enter the revised information in the computer and send you a new flow sheet. The intent is to help you by providing guideline-directed care for better patient outcomes.

Periodically, you may receive reports on your own practice compared to your peers. These reports are confidential and can be sent only to you. Both your identification and all patient identifiers are removed and aggregate data on all patients in Canada is presented.

Give it a try and give us your feedback.

How to reach us:
Canadian Centre for Research on Diabetes
Tel: 1-800-717-0145
Fax: (613) 283-9020
Toll-free fax: 1-866-696-4099
E-mail: diabetes@igs.net
<table>
<thead>
<tr>
<th>Date</th>
<th>Note</th>
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</table>

**NOTES**

ALT if on TZD
CK if on Statin
Hgb
WBC
Urine Glu
Urine Prot
Urine Ketone
Phys. Activity
Neuro Exam
Diet
Other

**Medication Dose**

<table>
<thead>
<tr>
<th>Start Date</th>
<th>Stop Date</th>
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<tbody>
<tr>
<td>dd-mm-yy</td>
<td>dd-mm-yy</td>
</tr>
</tbody>
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**Weight / Lb**

**Weight / KG**

**BMI**

- from 20 to 25

**Blood Pressure**

- Systolic < 130
- Diastolic < 80

**Waist Circ**

- M < 40 in, F < 36 in
- M < 100 cm, F < 90 cm

**Fasting Blood Sugar (FBS)**

- < 7 mmol/L

**PC GLU**

- < 10 mmol/L

**Average Glu**

- < 7 mmol/L

**A1c**

- < 7%

**3 mo**

**Blood Cholesterol (Chol)**

- HDL
- TC/HDL < 4
- LDL < 2 mmol/L
- Trig < 1.5 mmol/L

**10 yr Heart Disease Risk**

- UKPDS

**Lipids**

- MAU < 20 mg/L
- ACR M < 2, F < 2.5
- Creatinine < 120 mmol/L
- Cr Clearance > 90 mL/min

**Dietician**

- Y or N at diagnosis

**Family History**

- Diabetes: Yo r N
- Heart: Yo r N

**Diabetes Education**

- Y or N
- Year

**Smoker**

- Yo r N
- Ex Smoker: Yo r N
- Since: Year

**DIAGNOSIS:**

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

**Other**

**Name:** first name      last name

**Address:** street address

**City:** city

**Prov:** prov

**PC:** postal code

**Phone:** phone          Fax: fax

**DOCTOR**

**PATIENT**