Clinical Focus:

Advances in the Treatment of Diabetes

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Pharmacological Management of Type 2 Diabetes

The Diabetes Screening in Canada (DIASCAN) study[1] showed us that, although only 6% of the Canadian population has diabetes, almost one-quarter of the patients seen in a typical family physician's office have the disease, showing the high burden of disease. Many of these patients come in with other complaints, such as hypertension or heart disease and one-third of them don't know they have diabetes. Furthermore, we have recognized that more than half of the population has the metabolic syndrome, giving them an increased cardiovascular risk profile. The Diabetes in Canada Evaluation (DICE) study[2] tells us that 50% of patients with diabetes in Canada do not achieve target levels of glucose control (A1C <7%), nor do they achieve targets for blood pressure (<130/80 mmHg) or lipids (LDL <2 mmol/L, TC/HDL <4).

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This is a poor statistic, given that the Canadian Diabetes Association's Clinical Practice Guidelines[3] clearly outline an objective, evidence-based road map for treatment. Moreover, we have a range of options in the diabetes treatment toolbox at our disposal. Lately, that toolbox has expanded through research that has resulted in both new understandings of disease mechanisms and new medications. Learning which agents work in which patients — and when to use them — should help us to improve diabetes care in Canada.

DISEASE MECHANISMS

Physiological glycemic regulation ensures adequate provision of glucose to the brain and other glucose-dependent tissues, while protecting our proteins from above-normal glucose levels.

Glucose levels are regulated through a delicate balance of glucose production and utilization. Glucose is made available by the digestion and absorption of carbohydrates, and is also produced in the liver during both the post-absorptive and fasting states through the breakdown of hepatic glycogen (glycogenolysis) and the formation of glucose from protein and fat sources (gluconeogenesis).

The pancreatic islet hormones insulin and glucagon function to maintain the balance between glucose production and utilization in the normal individual. Other hormones affect this balance in response to the stress of infection, trauma or dehydration, as well as during treatment with certain medications (e.g. glucocorticoids).

What goes wrong in type 2 diabetes?

People at risk for developing type 2 diabetes are often sedentary and overweight. Excessive visceral fat is a significant risk factor — this tissue is metabolically active and affects glucose homeostasis by increasing or decreasing production of fat cell products called lipokines. These abnormalities can lead to an insulin-resistant state long before hyperglycemia is detected. Compensation for insulin resistance through increased insulin secretion initially results in normal glucose levels, in both the fasting and postprandial states. Gradually, however, a loss of pancreatic beta cells leads to hyperglycemia — initially in the postprandial phase, then later in the fasting state. As the metabolic abnormalities of diabetes progress, lipotoxicity and glucotoxicity (increased levels of circulating fatty acids and glucose, respectively) have detrimental effects on beta cell insulin secretion. The same metabolic abnormalities further enhance insulin resistance.

Data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that, upon entry into the study, people with newly diagnosed type 2 diabetes had only 50% of their beta cell function remaining.[4] During the six-year follow-up, beta cell function continued to decline. If we assume that this loss follows a linear pattern, we can predict that beta cell function in these individuals had not been normal for more than a decade prior to enrolment.

A study of beta cell mass from autopsies of non-diabetic obese individuals (based on BMI criteria) and non-diabetic lean individuals[5] showed that the obese group had substantially greater beta cell volume compared with the lean cohort, possibly as a compensatory mechanism by which the obese increased insulin secretion and beta cell mass in response to insulin resistance. Conversely, obese subjects with impaired fasting glucose (IFG) had decreased beta cell mass compared with those who had normal glucose tolerance. Both the obese and the lean individuals with type 2 diabetes had beta cell masses lower than those of either group of non-diabetic subjects, indicating that there is indeed an association between diabetes and beta cell mass.

Clinically, these abnormalities result in a gradual increase in glycemia as described above.

Gastrointestinal hormones: the incretins

The gastrointestinal (GI) hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide) have recently been the subjects of intense research.

These two hormones belong to the incretin family — GI hormones secreted in response to food intake and rising plasma glucose levels. In normal physiology, food intake or increased plasma glucose results in their rapid secretion from cells in the small intestine. Secretion of GLP-1 starts a long time before nutrients reach the distal small bowel (where GLP-1 is secreted), raising the possibility that there are neural or hormonal mediators secreted from the proximal gut or elsewhere that act upon GLP-1-producing cells. The differences between GLP-1 and GIP actions are described in Table 1.

In patients with type 2 diabetes, the incretin effect is reduced; insulin response to hyperglycemia is suboptimal, while glucagon levels are elevated and are not suppressed when blood glucose levels rise. Although GLP-1 and GIP both increase the insulin response to oral glucose ingestion, their metabolic effects are otherwise quite distinct. In contrast to GLP-1, GIP is ineffective in type 2 diabetes, and thus there is far less interest in GIP as a therapeutic intervention.

FP Review

Disease Mechanisms

The UKPDS[4] has indeed shown that diabetes is a progressive disease. The disease process starts a decade or so before the diagnosis is made, and is marked by increasing insulin resistance paralleled by increasing insulin production in order to maintain normal glucose control. As insulin needs increase, the pancreas reaches a point where it can no longer meet demand; beta cells then begin to fail while glucose levels begin to rise. When the fasting glucose exceeds 7 mmol/L or when the postprandial level exceeds 11.1 mmol/L, we can confirm the diagnosis of diabetes. By this stage, 75% of insulin sensitivity and 50% of the ability to produce insulin has been lost. One of the first changes we see is loss of first-phase insulin secretion, as well as loss of glucagon suppression with hyperglycemia. Some of these changes reflect a decrease in incretin levels. As more beta cell function is lost, progressive insulin deficiency increases.

Screening for diabetes using an FPG test should be performed every three years in individuals >40 years of age. Earlier screening should be considered in those people with risk factors for diabetes. The CDA diagnostic criteria can be summarized as follows:

TABLE 1

CDA criteria for the diagnosis of diabetes

Fasting plasma glucose
(no caloric intake for at least 8 hours) ≥7.0 mmol/L

OR

Casual plasma glucose
(any time of day, regardless of interval since last meal) ≥11.0 mmol/L PLUS
Classic symptoms of diabetes (e.g. polyuria, polydipsia, unexplained weight loss)

OR

Two-hour plasma glucose
in a 75 g oral glucose tolerance test ≥11.0 mmol/L

NB: A confirmatory laboratory glucose test must be done on another day unless there is unequivocal hyperglycemia and acute metabolic decompensation.

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TABLE 1

Overlapping and contrasting actions of GLP-1 and GIP

GLP-1	GIP
Released from L cells in ileum and colon	Released from K cells in duodenum
Stimulates insulin release from beta cells	Stimulates insulin release from beta cells
Potent inhibition of gastric emptying	Modest effect on gastric emptying
Potent inhibition of glucagon secretion	No significant inhibition of glucagon secretion
Reduction of food intake and body weight	No significant effects on satiety or body weight
Significant effects on beta cell growth and survival	Potential effects on beta cell growth and survival
Insulinotropic actions preserved in type 2 diabetes	Defective insulinotropic action in type 2 diabetes

Adapted from: Drucker DJ. *Diabetes Care* 2003;26:2929-2940.

Use of incretin preparations in treatment of type 2 diabetes

The discovery of the role that incretin hormones play in the physiology of carbohydrate metabolism, modulation of appetite and gastric motility made these agents therapeutic targets for the treatment of type 2 diabetes and possibly for the preservation of beta cell function.

The pharmacokinetic profile of plasma GLP-1 following a single 1.5 mmol/kg subcutaneous injection has been studied in human subjects with type 2 diabetes. The levels of total immunoreactive GLP-1 (representing both intact and bio-inactive degraded forms of the peptide) were subsequently elevated for up to three hours. In contrast, circulating levels of intact bioactive GLP-1(7-36) amide were only transiently increased and returned to baseline within 60 minutes of injection. The transient appearance and rapid elimination of GLP-1 in plasma is attributable to a combination of enzymatic degradation and renal clearance.

Following meal ingestion, levels of intact GLP-1 and GIP rise rapidly in the portal circulation, and within minutes levels of both incretins are transiently increased in the systemic circulation. Both GLP-1 and GIP are substrates for the enzyme dipeptidyl peptidase-4 (DPP-4), which cleaves and inactivates both peptides at the position 2 alanine. Inhibition of this enzyme using DPP-4 inhibitors prolongs the circulating half-life of intact bioactive GLP-1 and GIP from the normal one of two minutes to 24 hours and reduces the generation of the metabolites GLP-1(9-36) amide and GIP(3-42).

Because of the very short circulating half-life of GLP-1, its use as a native hormone in the treatment of type 2 diabetes would necessitate its administration as a continuous intravenous infusion to attain therapeutic action. This is clearly impractical.

The search for analogues that mimic GLP-1 action with less vulnerability to DPP-4 enzyme breakdown or for means of prolonging the action of GLP-1 have so far resulted in two injectable preparations with relatively long-acting effect:

Exenatide is a potent agonist of GLP-1 receptor. It is resistant to inactivation by DPP-4 and is more potent than GLP-1. The structure of exenatide carries 50% identity with human GLP-1.[6, 7, 8]

Liraglutide is a modified GLP-1 molecule to which a palmitoyl fatty acid side chain has been added. This improves its pharmacokinetics by allowing reversible albumin binding, thus slowing its absorption and its degradation by DPP-4 inhibitors.

In clinical use, exenatide (Byetta) is administered via subcutaneous injection twice daily, while liraglutide is injected only once daily. Both preparations are associated with improved blood glucose control, weight loss and decreased appetite. The most common side-effects are nausea and vomiting. These products are not yet available in Canada.

DPP-4 inhibitors

Another method of increasing circulating levels of GLP-1 is to interfere with their breakdown by blocking the DPP-4 enzyme responsible for rapid inactivation of GLP-1.

DPP-4 inhibitors are oral medications that have been successfully used in the treatment of type 2 diabetes in clinical studies. Three members of this group have been formulated: saxagliptin, sitagliptin and vildagliptin. To date only sitagliptin (Januvia) is available for clinical use in Canada.

Pharmacological evidence for the importance of DPP-4 in the control of GLP-1 degradation is evident from studies analyzing the proportion of intact versus degraded GLP-1 in pigs. The majority of circulating GLP-1 is rapidly degraded to bioinactive GLP-1(9-36) amide in the absence of DPP-4 inhibition. In contrast, infusion of GLP-1 in the presence of the DPP-4 inhibitor valine-pyrrolidide (Val-Pyr) results in preservation of levels of intact GLP-1(7-36) amide.

The DPP-4 inhibitors are capable of reproducing most of the biologic actions of the incretin hormones in persons with T2DM (see Table 2).

Following sitagliptin administration, plasma DPP-4 activity increases in a dose-dependent fashion. Dose-ranging studies revealed that the reductions in A1C were similar with sitagliptin 50 mg once daily, 100 mg once daily and 50 mg twice daily. Subsequent studies have shown greater reductions with 100 mg once daily than 50 mg once daily. This was, therefore, the dose carried forward in the subsequent studies.[9] The drug is available in Canada in the 100 mg formulation. As with other oral antihyperglycemic agents, the degree of glucose lowering was dependent on baseline A1C levels with an average 1.13% reduction if baseline A1C was >8.5%.

Effect on glucose parameters and beta-cell function

A 24-week double-blind, placebo-controlled monotherapy study comparing 100 mg to 200 mg sitagliptin once daily in 750 patients with type 2 diabetes and a baseline A1C of about 8% was conducted.[10] Whereas the A1C increased in

TABLE 2

Type 2 diabetes (T2D) and biological actions of GLP-1 and DPP-4 inhibitors

Features of T2D	GLP-1 in T2D	DPP-4 inhibitors
Defective glucose-stimulated insulin secretion	Glucose-dependent stimulation of insulin secretion	Yes
Slow insulin secretory response to meals	More adequate insulin response after meals	Yes
Hyperglucagonemia	Suppression of glucagon secretion	Yes
Reduction or absence of incretin effect	Replacement of incretin activity, greater incretin effect	Not tested, but probable
Reduced beta cell insulin content	Increased synthesis of proinsulin	Yes
Reduced endocrine beta cell mass	Increase in pancreatic islet beta cell mass	Yes

those subjects receiving placebo, both doses of sitagliptin significantly improved glycemia to a similar degree (A1C reduction of 0.79% and 0.94% from baseline). Body weight decreased by 1.1 kg in the placebo group, presumably due to continuing hyperglycemia. There was no weight increase in the active treatment groups, despite improved glucose levels. Sitagliptin was also associated with greater reductions in postprandial versus fasting glucose levels (see Figure 2).

In the same study, beta cell function was assessed by the proinsulin/insulin ratio and HOMA–ß, and showed significant improvement. This could be related to improved glucose levels and decreased glucotoxicity of the beta cells or to a direct effect of the drug on the beta cell.

Combination with metformin

When added to ongoing metformin therapy (> 1500 mg/day), sitagliptin 100 mg daily was compared to placebo in 650 patients with type 2 diabetes and baseline A1C of about 8%. Patients in this trial[11] were followed for 24 weeks. Sitagliptin therapy was associated with a significant reduction in A1C (0.65%, $p<0.001$), which reached steady-state after about 18 weeks; 47% of patients on sitagliptin reached A1C <7%, compared to only 18% in the placebo group.

Combination with pioglitazone

The safety and efficacy of sitagliptin 100 mg once daily versus placebo added to background pioglitazone (Actos) therapy (30 mg to 45 mg daily) has also been studied.[12] Over 24 weeks in more than 330 subjects with type 2 diabetes (mean A1C of about 8%), sitagliptin therapy was associated with a significant reduction in A1C of 0.7%; 45% of patients in the active treatment group reached A1C of <7%, compared to only 23% in the placebo group.

Comparative study: sitagliptin vs. glipizide

The safety and efficacy of sitagliptin 100 mg daily versus the active comparator glipizide (a sulfonylurea not available in Canada) 5 mg to 10 mg daily over 52 weeks was studied in 1,172 subjects with type 2 diabetes.[13] All participants were inadequately controlled on metformin, with a mean A1C of 7.5%. Sitagliptin showed comparable reduction in A1C to glipizide when added to metformin therapy. As would be expected from studies with other oral hypoglycemic agents, the degree of glucose lowering was dependent on baseline glycemic control with a mean reduction in A1C of about 1.7% in those subjects with a baseline A1C of >9%. In this study, sitagliptin provided weight reduction of 1.3 kg versus a weight increase of 1.2 kg with glipizide, and a much lower incidence of hypoglycemia (4.9% vs. 32%).

Co-administration of sitagliptin + metformin as initial therapy in type 2 diabetes

The safety and efficacy of sitagliptin 100 mg daily administered in combination with metformin as initial therapy relative to sitagliptin or metformin monotherapy over 24 weeks was also studied. More than 1,000 subjects with type 2 diabetes and a mean A1C of 8.8% took part.[14] Note that in Canada sitagliptin is only approved for use in combination with metformin.

The combination of sitagliptin 50 mg plus metformin 1,000 mg twice daily was associated with a 2.1% reduction in A1C. The degree of glucose lowering across the therapies was not statistically compared, as a variable number of patients per group had been washed out of prior oral hypoglycemic therapy. In a group of patients who were not randomized (because their baseline A1C was above the entry criterion of 11%) and who were treated with open-label sitagliptin 50 mg plus metformin 1000 mg twice daily, a 2.9% reduction in A1C and a 7.3 mmol/L reduction in FPG levels were observed.

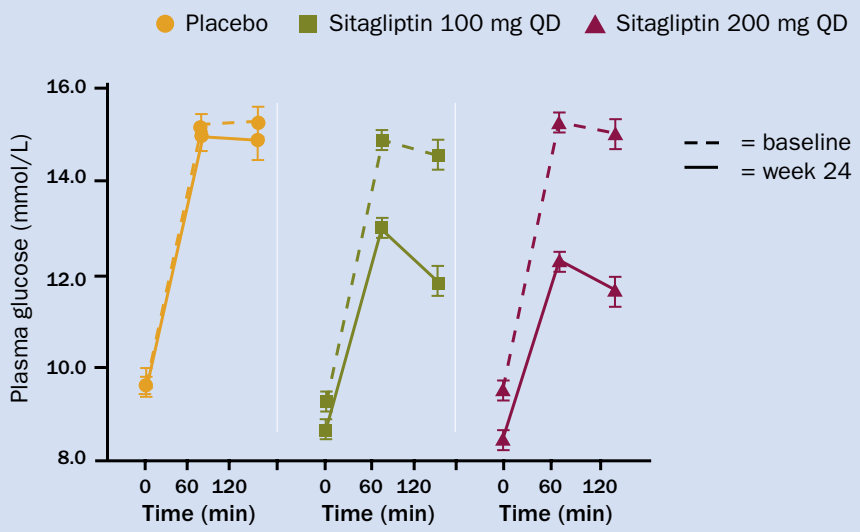
Sitagliptin added to glimepiride alone or glimepiride plus metformin in patients with type 2 diabetes

The effects of sitagliptin 100 mg daily when added to glimepiride (Amaryl) >4 mg daily plus metformin >1500 mg daily was also studied in 441 subjects. This was the first trial to include sitagliptin as part of triple therapy. Overall, sitagliptin reduced A1C by 0.74%. The reduction was 0.57% in Stratum 1 (those on glimepiride alone) and 0.89% in Stratum 2 (those on glimepiride plus metformin).

Table 3 summarizes clinical trial and safety data for sitagliptin.

FIGURE 2

Post-meal glucose responses to sitagliptin monotherapy for 24 weeks



Difference in LS mean 2-hr PPG change from baseline vs. placebo at week 24
Sitagliptin 100 mg QD = -2.6 mmol/L; $p<0.001$
Sitagliptin 200 mg QD = -3.0 mmol/L; $p<0.001$

Aschner P, et al. *Diabetes Care*. 2006;29:2632–2637.

TREATMENT

The CDA's 2003 Clinical Practice Guidelines emphasize the importance of attaining and maintaining glycemic control as early as possible after diagnosis. Lifestyle modifications are indicated as an initial approach without medications if glycated hemoglobin (A1C) levels are below 9% at diagnosis. If glycemic targets (A1C <7%; pre-meal glucose 4 to 7 mmol/L; two-hour post-meal glucose 5 to 8 mmol/L) are not reached, or if initial A1C is greater than 9%, pharmacotherapy is initiated concurrent with lifestyle interventions.

Metformin is the recommended first-line medication in practice guidelines worldwide, given its proven glycemic lowering effect, the durability of its glycemic control and its safety and side-effect profile. Metformin is the only antihyperglycemic agent proven to decrease all diabetes-related endpoints according to UKPDS data in overweight patients. It also decreased myocardial infarction in the same group when compared with conventional treatment.

If A1C is >9% at presentation or if glycemic targets are not achieved with metformin within two to three months, other agents should be added. The decision about which agent(s) to employ is made on a case-by-case basis, taking into account the pros and cons of each medication group.

The use of antihyperglycemic agents in clinical practice

To address the positioning of incretin preparations in the treatment algorithm for type 2 diabetes, a review of available antihyperglycemic agents is warranted.

Alpha-glucosidase inhibitors (AGIs)

Complex carbohydrates from the diet are cleaved into oligosaccharides and disaccharides in the duodenum by pancreatic amylases, but these must be further broken down to monosaccharides by brush border enzymes, the alpha glucosidases, in order to be absorbed. This process is rapid and efficient, and most carbohydrates are digested and absorbed in the upper segment of the jejunum, with little carbohydrate reaching the distal jejunum or ileum. AGIs were developed to delay intestinal absorption of carbohydrates. Acarbose (Glucobay) is the only AGI available in Canada.

The AGIs bind competitively to the carbohydrate-binding region of alpha-glucosidase enzymes, thereby competing with oligosaccharides and preventing their cleavage to absorbable monosaccharides. Co-administration of AGIs with carbohydrate slows the digestion of the carbohydrates and delays their absorption. The delayed absorption of carbohydrates from the proximal jejunum decreases the postprandial rise in blood glucose.

Characteristics:

- Dose: 50 mg to 100 mg with the first bite of each meal; usually three times per day.
- Reduces A1C by about 0.5% to 0.8%. Negligible risk of hypoglycemia.
- Not recommended as initial therapy in people with severe hyperglycemia (A1C ≥9.0%).
- Often used in combination with other oral antihyperglycemic agents.
- Weight-neutral as monotherapy.
- Most common side-effects are bloating, increased intestinal gas and abdominal cramping. Discontinuation rate is high (up to 60% in studies) due to the GI side-effects.
- Contraindicated in chronic renal failure and with inflammatory bowel disease.

Biguanides

Metformin is the only biguanide available worldwide. The mechanism of action is not well understood. Hepatic glucose production is decreased with its use, thereby decreasing fasting glucose levels. It also has an insulin-sensitizing effect, which mildly reduces insulin resistance. Recently, the use of metformin has been found to increase GLP-1 levels, especially when used in conjunction with the DPP-4 inhibitor sitagliptin.

Characteristics:

Dose: 500 mg to 2000 mg per day, given in a divided dose twice daily. Note that the *Compendium of Pharmaceuticals and*

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Specialties lists the maximum dose as 2500 mg, but research has shown that doses greater than 2000 mg do not add more benefit in glycemic control. Metformin should be taken during or after meals. Multiple daily dosing is needed due to its short half-life. This may decrease compliance. A long-acting formulation (Glumetza) is available in 500 mg and 1000 mg, and can be given once daily. When metformin is used in monotherapy, there is no risk of hypoglycemia.

- Improved cardiovascular outcomes in overweight subjects.
- Contraindicated if CrCl/eGFR <30 mL/min and in hepatic failure.
- Caution if CrCl/eGFR <60 mL/ min.
- Weight-neutral as monotherapy; promotes less weight gain when combined with other antihyperglycemic agents, including insulin.
- Improved glycemic control and less insulin needed when combined with insulin.
- Side-effects are mainly gastrointestinal (nausea, abdominal discomfort and diarrhea).
- About 20% of patients using metformin have decreased vitamin B12 absorption.
- Lactic acidosis is extremely rare, and is usually restricted to using the drug in patients with end-stage renal disease or severe dehydration.

Insulin secretagogues

Sulfonylureas: gliclazide (Diamicron, Diamicron MR), glimepiride (Amaryl), glyburide, others. Sulfonylurea drugs induce the release of insulin by binding to sulfonylurea receptors in the cell membrane of the beta cells. This results in closure of the KATP channels present in the cell membrane of pancreatic beta cells and prevents K+ efflux through the channel pore, leading to membrane depolarization, and opening of voltage-sensitive Ca2+ channels, which allows influx of calcium and, in turn, the release of insulin through exocytosis.

Non-sulfonylureas: repaglinide and nateglinide. Short-acting preparations given just before meal ingestion. The mechanism of insulin release with repaglinide seems to be similar to the sulfonylureas.

Repaglinide (Gluconorm): Dose range: 0.5 mg to 4 mg before meals; maximum dose 16 mg/day. Mostly excreted in the bile. Half-life not altered in renal dysfunction.

Nateglinide (Starlix): Dose 120 mg given just before meal ingestion. Has the potential to lower A1C by 0.5%.

Characteristics:

- Relatively rapid BG-lowering response.
- Least glycemic durability.
- All insulin secretagogues, except nateglinide, reduce glycemia by a similar degree.
- Postprandial glycemia is especially reduced by repaglinide and nateglinide.
- Hypoglycemia and weight gain are especially common with glyburide.
- Consider using other classes of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure).
- If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia and glimepiride is associated with less hypoglycemia than glyburide.
- Most sulfonylureas should be avoided in moderate to severe renal failure (eGFR <30 mL/min) because of active metabolites that may contribute to hypoglycemia. Gliclazide, because it does not have active metabolites, may be used with eGFR as low as 15 mL/min. Repaglinide can also be used in patients with impaired renal function.
- Repaglinide and nateglinide are associated with less hypoglycemia in the context of missed meals.

Thiazolidinediones

Thiazolidinediones (TZDs) have far-reaching effects on adipose tissue, beta cells, vascular endothelium, muscle cells, liver and kidneys. Their actions include increased glucose disposal by increasing uptake of glucose by muscle and fat tissue.

TZDs available: pioglitazone (15 mg to 45 mg once daily); rosiglitazone (Avandia) (4 mg to 8 mg once daily); combination of rosiglitazone and metformin in varying doses.

Characteristics:

- Increase insulin sensitivity.
- Decreased free fatty acids (FFA).
- Increased adiponectin.
- Preservation of beta cell mass (in animal studies).
- Vascular & anti-inflammatory effects.
- Longer durability of glycemic control with monotherapy compared to metformin or glyburide.
- Mild BP lowering.
- Require six to 12 weeks to achieve full glycemic effect.
- Weight gain (waist-to-hip ratio not increased).
- May induce edema and/or heart failure in persons with compromised heart function.
- Avoid in patients with any degree of heart failure.
- Higher rates of heart failure when combined with insulin.
- Rare occurrence of macular edema.
- Rare occurrence of fractures in females.
- Suggestion of increased risk of cardiovascular events with rosiglitazone unsubstantiated.

Insulin

Insulin treatment provides replacement for the insulin insufficiency that constitutes an integral part of the pathogenesis of type 2 diabetes. Insulin can control diabetes in almost all cases. It acts by reducing hepatic glucose production, reducing lipolysis and proteolysis, and enhancing insulin-mediated glucose uptake.

Formulations:

- Rapid-acting analogues: aspart (NovoRapid), Lispro (Humalog).
- Short-acting: regular (Humulin-R, Novolin ge Toronto).
- Intermediate-acting: NPH (Humulin-N, Novolin ge NPH).
- Long-acting basal analogues: detemir (Levemir), glargine (Lantus)
- Premixed: Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50)
- Biphasic insulin aspart (NovoMix 30)
- Insulin lispro/lispro protamine (Humalog Mix25 and Mix50)

Therapeutic considerations:

- Potentially greatest A1C reduction and no maximal dose.
- Numerous formulations and delivery systems allow for regimen flexibility.
- Hypoglycemia risk highest with regular and NPH insulin.
- When initiating insulin in patients with type 2 diabetes, consider adding bedtime intermediate-acting insulin or long-acting insulin analogue to daytime oral antihyperglycemic agents (although other regimens can be used).
- Intensive insulin therapy regimen recommended if above fails to attain glycemic targets.
- Increased risk of weight gain relative to sulfonylureas and metformin.
- Premixed insulin regimens can provide adequate glycemic control in selected patients.

PREVENTING COMPLICATIONS

Long-term complications of diabetes include retinopathy, nephropathy and neuropathy (microvascular complications) and coronary heart disease, diabetic cardiomyopathy, cerebrovascular disease and peripheral arterial disease (macrovascular complications).

The association between hyperglycemia and microvascular disease has been proven by the results of the Diabetes Control & Complications Trial (DCCT) in type 1 diabetes and the UKPDS in type 2 diabetes. In a follow-up of the DCCT, it also became clear that glycemic control early on in the course of type 1 diabetes results in significant decrease in macrovascular disease.

Vascular protection is advocated for high-risk patients with diabetes (most patients) through:

1. Glycemic control (A1C <7% & control of postprandial glucose levels)
2. Lipid control: LDL <2 mmol/L; cholesterol/HDL ratio <4
3. Control of blood pressure: <130/80 mmHg
4. ACE inhibition when indicated
5. Anti-platelet therapy in high-risk patients

In type 2 diabetes, the Steno-2 study proved that a multi-faceted approach (glucose, lipid and blood pressure control, ACE inhibitors and ASA) to treatment of patients with type 2 diabetes and increased urinary albumin excretion resulted in significant decrease in

TABLE 3

Summary of clinical studies of sitagliptin

Sitagliptin once daily monotherapy:

Substantially improved glycemic control (A1C, FPG, PPG)

- Greater proportion pts achieved A1C targets
- Greater A1C reduction with higher baseline A1C
- Improved beta cell function

Demonstrated overall safety and tolerability similar to placebo

- Slightly higher incidence of mild GI side-effects
- Low incidence of hypoglycemia, similar to placebo
- No change in body weight relative to baseline

Combination sitagliptin + metformin as initial therapy:

Marked reductions in mean A1C

- Up to 2.1% reduction relative to placebo in randomized cohort
- Nearly 3% reduction from baseline in open-label cohort

Up to 66% of patients achieved A1C <7%

Generally well tolerated, similar incidence of GI side-effects as metformin monotherapy

FP Review

Treatment

Insulin resistance and loss of first-phase insulin secretion is the predominant defect in the early stages of diabetes. Treatments therefore are directed toward improving insulin resistance, decreasing insulin needs and reducing hyperglucagonemia. With disease progression, insulin deficiency predominates and treatment options become more insulin-focused.

The UKPDS showed a progressive decline in beta cell function, irrespective of treatment with metformin, sulfonylureas or insulin, the standard treatments of the time. More recently, treatment with TZDs has demonstrated pancreatic preservation in animal studies and longer durability of glycemic control in monotherapy, compared to glyburide and metformin. The new incretin enhancers also show some promise of improving pancreatic beta cell function in human and animal studies, and preventing beta cell death in animal studies.

Medication regimens must be individualized, balancing the potential for lowering A1C against cost, adherence, safety and side-effects.

Step 1: Treatment always starts with changes in diet and exercise. Patients should be referred to a dietitian and appropriate educational programs. If these measures do not achieve adequate control in three months, medication should be added. In patients with A1C >9%, two simultaneous treatments are indicated, since neither alone is likely to reduce A1C by more than 1% to 1.5%.

Metformin, the most common first-line drug, increases insulin sensitivity and decreases glucose burden by reducing glucose production from the liver. Sometimes associated with GI side-effects such as nausea and diarrhea, it does not cause weight gain or hypoglycemia. It should not be used in moderate to severe renal failure (eGFR <30 mL/min) and should be used with caution in patients with eGFR of 30 to 60 to decrease the remote possibility of lactic acidosis. We start with small doses of 250 mg to 500 mg once (long-acting preparation) or twice daily in order to minimize side-effects, titrating up to the full therapeutic dose of 1000 mg twice a day. Doses in excess of 2000 mg do not improve glycemic effect and usually result in increased GI side-effects.

Step 2: If we cannot achieve target levels of glycemia with lifestyle intervention alone or with metformin, adding a second agent is prudent. We must consider complementary mechanisms of action and where the patient is on the continuum of pancreatic insufficiency.

The TZDs and, potentially, the incretin enhancers may offer some measure of pancreatic protection. Pioglitazone and rosiglitazone decrease glucose load by increasing insulin sensitivity and glucose uptake in fat and muscle. On their own, they do not cause hypoglycemia. They tend to be associated with some weight gain and may cause increased fluid retention and edema. They should not be used in patients with any degree of heart failure, as they can increase fluid load that leads to congestive cardiac failure. TZDs are not approved in Canada for use in combination with insulin, given the increased potential for fluid retention and the risk of CHF.

In type 2 diabetes, incretin levels are reduced, leading to loss of first-phase insulin secretion and a lack of suppression of glucagon secretion with increased glucose levels. Incretins are rapidly broken down by the DPP-4 enzyme, but DPP-4 inhibitors increase blood levels of these hormones to normal physiologic levels.

The only DPP-4 inhibitor approved in Canada is sitagliptin, available in a 100 mg tablet to be taken once daily with metformin. This combination can lower A1C by 1% to 1.5%. In monotherapy, sitagliptin lowers A1C by 0.8% to 0.9%. There is no increased risk of hypoglycemia when used as monotherapy or in combination with metformin and no associated weight gain. The drug is metabolized and excreted by the kidney, thus is not indicated in cases of moderate to severe renal failure (eGFR <30 mL/min).

Secretagogues increase endogenous insulin output, thereby lowering glucose levels. The sulfonylurea glyburide is best known; gliclazide tends to cause less hypoglycemia in the elderly. The meglitinides have particular value in people who have irregular mealtimes, as they are very short-acting secretagogues and are given only with meals.

Insulin can be used at any stage of treatment for type 2 diabetes, but becomes more essential with decreasing endogenous insulin levels. Insulin should be used if marked hyperglycemia or metabolic decompensation is present. We usually start with a bedtime dose of intermediate- or long-acting insulin, then titrate up to achieve normal fasting glucose levels. If A1C remains high because of postprandial hyperglycemia despite normal fasting glucose levels, full basal/bolus insulin may be needed.

Medications with complementary mechanisms of action are added to achieve control. Although no manufacturers have applied to Health Canada for an indication of triple or quadruple combination therapy, such approaches are frequently used. However, we discontinue TZDs when we start insulin and usually stop secretagogues if we are treating with multiple daily injections.

People with type 2 diabetes may receive prescriptions for as many as 10 different medications, several of which may be dosed at different times. Adherence is therefore a challenge. We must make medication directions as simple as possible, preferably dosing no more than twice a day while offering tools such as dosettes or pre-packaged medications.

mortality from cardiovascular causes and of cardiovascular events generally. There was also significant decrease in microvascular complications.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized >10,000 patients at high risk for myocardial infarction and stroke, diagnosed with type 2 diabetes for an average of 10 years and either a history of CV disease or the presence of two other risk factors for arteriosclerotic heart disease into an intensive glycemic control group (A1C target <6%) or to standard treatment (A1C target of 7% to 7.9%). Patients were treated with all available antihyperglycemic agents at the discretion of the treating physician to attain treatment targets.

On February 6, 2008, the Data Safety Monitoring Board stopped the glycemic arm of the study 18 months ahead of schedule (but continued the blood pressure and lipid arms) because of increased mortality in the intensive treatment group.

Researchers for the Action in Diabetes and Vascular Disease: Preterax [sold in Canada as Coversyl Plus] and Diamicron MR Controlled Evaluation (ADVANCE) study, which enrolled more than 11,000 participants with characteristics similar to those in the ACCORD study, recently analyzed their data and found no increase in CV mortality in the intensive glycemic control group (average A1C of 6.4%). The intensive treatment group gave gliclazide MR for all patients, and a range of other drugs for those not reaching target blood glucose levels.

We therefore need to emphasize several points:

1. Patients with type 2 diabetes should be treated to target A1C <7%, because this was shown in the UKPDS to decrease microvascular and macrovascular disease in a study of >10-year duration.
2. Treatment goals should be directed to the individual taking into account the characteristics of therapeutic interventions and patient's co-morbidities.
3. In patients with type 2 diabetes of long duration and with high risk of cardiovascular disease, caution should be taken to not intensify glycemic control below the A1C 7% target, especially if there is a tendency for recurrent hypoglycemia.
4. Patients should not change treatment nor stop anti-hyperglycemic agents on their own, but should discuss treatment regimens with their diabetes team.

QUALITY OF LIFE ISSUES

As a chronic disease associated with increased morbidity and shorter

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lifespan, diabetes has a significant effect on quality of life (QOL). Depression is associated with hyperglycemia in patients with type 1 or 2 diabetes. It is present in > 25% of patients, and has adverse effects on functioning and QOL.[15] Furthermore, the effect of depression on QOL is more significant in people with diabetes compared to non-diabetic individuals.[16]

Other effects on QOL relate to the disease's effect on general well-being, employment capacity, the ability to maintain medication vigilance, follow a good diet, quit smoking and exercise. Decreased energy, increased health care expenditure (including out-of-pocket expenses), discrimination, complicated treatment regimens and guilt can also negatively impact diabetes sufferers. Sadly, this list is not exhaustive.

Data suggest intensive medical treatment of diabetes and co-morbidities significantly improves QOL compared with controls. Ménard and colleagues found that QOL was not affected by complications or hypoglycemic episodes, and that scores improved in patients who began insulin treatment during the study.[17] The authors concluded that QOL improved significantly, despite the inherent constraints imposed by intensive medical treatment.

In another study in the primary-care setting, patients treated with insulin reported higher diabetes-related emotional distress compared with oral- or diet-treated patients.[18] However, the greater distress was largely explained by greater disease severity and self-care burdens. There seems to be no contradiction between these two studies, which suggests that high disease burden results in poor quality of life and that intensive medical and lifestyle intervention improves QOL parameters.

A study on the effectiveness of antidepressants in patients with mild depression scores demonstrated no clear QOL or glycemic control benefit in patients with type 2 diabetes treated with paroxetine compared with placebo.[19] The study indicated that any possible benefit from administration of paroxetine in diabetic patients with mild depression is likely to be modest and of short duration. Routine antidepressant prescription for patients with diabetes and sub-threshold depression is not indicated.

The take-home message is that depression and type 2 diabetes frequently coexist and often go unrecognized. As Dr. Conway pointed out in a recent editorial, there are many barriers to effective care of the person with diabetes — the failure to recognize and treat co-existing depression should not be one of these.

PROGNOSIS

The therapeutic choices for treating hyperglycemia include lifestyle measures, metformin, incretin enhancers, TZDs, insulin secretagogues, acarbose and insulin. Each of these tools has a role to play in treatment, but practitioners must recognize the unique contributions that each can make.

Glycemic control of A1C to less than 7% is a cornerstone of diabetes treatment. By early, aggressive and effective use of the tools we have, and the subsequent treatment of comorbidities, we can advance diabetes care and provide an improved quality and quantity of life to our patients. Treatment is multifactorial, involving not only glucose control, but also blood pressure treatment to <130/80 mm Hg, vascular protection with ACE inhibitors, cardiovascular risk reduction with statins and thrombosis prevention with ASA. ●

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1 Case Study: Presentation

MR. R.C. IS A 50-YEAR-OLD ADMINISTRATIVE ASSISTANT WHOSE FATHER AND A BROTHER BOTH HAVE DIABETES. HIS FATHER HAD A MYOCARDIAL INFARCTION AT AGE 58. At his first visit three years ago, his random glucose was 11.8 mmol/L; a subsequent fasting glucose was 8.1 mmol/L. At that time, he weighed 226 lbs (102.7 kg) with a 5′10″ (178 cm) frame (BMI 32.5). He led a sedentary lifestyle. Blood pressure (BP) was 135/80 mmHg and other key lab values were: total cholesterol (TC) 5.3, HDL 0.9, LDL 3.2, triglycerides (Trig) 1.75 mmol/L and A1C 7.8%.

After lifestyle counselling, he was treated with an ACE inhibitor along with a statin, ASA for cardiovascular prevention and metformin 500 mg bid, which was increased two months later to 1 g bid. He was encouraged to lose 5% of total body weight — a goal he achieved — and he began to walk daily for exercise. His weight came down to 210 lbs and on metformin his A1C was 6.8%.

At his recent annual checkup, three years after diagnosis, his values are as follows:

Physical examination: Weight 218 lbs (99 kg); Height 5′10″ (178 cm); BMI 32.5; waist circumference 46″ (115 cm); BP 130/76 mmHg.

Laboratory investigations: FPG 8.1 mmol/L; A1C 7.5%; average glucose 10.5 mmol/L; TC 3.2 mmol/L; HDL 1.1 mmol/L; LDL 2.0 mmol/L; TC/HDL 2.90; Trig 3.60 mmol/L; urinary albumin/creatinine ratio (uACR) 1.8.

He had been doing well with diet, exercise and metformin, but over the past year has regained lost weight and his FPG levels have increased. He no longer walks every day. Although reinforcement of lifestyle changes with referral to a dietitian and a structured exercise prescription are needed, he also requires the addition of a second antihyperglycemic agent. He meets the criteria for metabolic syndrome and insulin resistance.

Treatment guidelines suggest several options, which should be discussed with the patient. Decisions should be made on a case-by-case basis. A TZD is considered, but there are concerns about the potential for further weight gain. We decide to add a DPP-4 inhibitor, as it tends to be weight-neutral and, in combination with metformin, can achieve the needed 1% reduction in AIC. Because the mechanisms of action are complementary, he will continue the full therapeutic dose of 2000 mg metformin daily.

FOLLOW-UP

After three months, Mr. R.C.'s glucose monitoring records show an average fasting glucose of 7.2 mmol/L. His A1C is 6.8% (a 0.7% reduction from previous), consistent with an average glucose of 9.0 mmol/L. He is managing to walk three days of the week and has achieved a three-pound weight loss. He is booked for a further A1C test in three months. ●

2 Case Study: Presentation

MRS. D.M. IS A 65-YEAR-OLD RETIRED NURSING ASSISTANT DIAGNOSED WITH DIABETES TWO YEARS AGO. SHE HAS HYPERTENSION AND DYSLIPIDEMIA, AND HER FATHER DIED AT AGE 52 FROM A HEART ATTACK. She is physically active and of normal weight. She had been treated with an ACE inhibitor but developed a cough so she was switched to an ARB/diuretic combination; she also takes simvastatin 40 mg once daily and EC-ASA 81 mg daily.

Three months after diagnosis she started metformin 500 mg twice daily; this was increased to 1000 mg twice daily six months later. Three months ago, with her A1C at 8%, glyburide 5 mg twice daily was added. She subsequently had a severe episode of hypoglycemia and was taken to hospital by ambulance. Because of this, gliclazide was substituted, but she had several subsequent hypoglycemic episodes during the night. She is very concerned about the hypoglycemia and is worried about further episodes if she continues the sulfonylurea.

Physical examination: Weight 148 lbs (67 kg); height 5′6″ (167 cm); BMI 24; BP 127/78 mmHg; home glucose monitoring shows average FPG 9.1 mmol/L; overall average glucose 11.2 mmol/L in the preceding month.

Laboratory investigations: FPG 9.4 mmol/L; A1C at 8% is consistent with average glucose of 11.5 mmol/L; TC 4.5 mmol/L; HDL 1.22 mmol/L; LDL 1.9 mmol/L; TC/HDL 3.7 mmol/L (target <4), Trig 1.40 mmol/L; random urine for albumin/creatinine ratio 2.4 mg/mmol.

She has not achieved adequate glycemic control on metformin but the addition of a sulfonylurea (SU) has resulted in serious hypoglycemia. The SU was changed from glyburide to gliclazide (which is associated with less hypoglycemia), and despite recurrent mild hypoglycemic episodes overnight, she has not achieved glycemic targets. Her A1C remains at 8% (target <7%), and she feels uncomfortable continuing the SU. We recommend adding a DPP-4 inhibitor (sitagliptin 100 mg once a day) because hypoglycemia is very unlikely when it is added to metformin. We expect a further 1% A1C reduction when combined with metformin (1000 mg twice a day), which should bring her to target glucose control.

FOLLOW-UP

Three months later, her A1C is 6.9%, showing adequate glycemic control with her current medications. ●

3 Case Study: Presentation

MS M.J. IS A 38-YEAR-OLD HAIRDRESSER WHO COMPLAINS OF FREQUENT URINATION WITHOUT BURNING BOTH DAY AND NIGHT. SHE HAS BEEN OVERWEIGHT FOR MANY YEARS AND HAS RECENTLY JOINED A SUPPORT GROUP. SHE FOLLOWS A VERY LOW-CALORIE DIET AND USES MEAL REPLACEMENTS. HER WEIGHT SUPPORT GROUP LEADER HAS RECENTLY ENCOURAGED HER TO JOIN A GYM WHERE SHE NOW WORKS OUT FOR A HALF-HOUR EVERY DAY.

Ms M.J. is a smoker and is afraid she will gain weight if she tries to quit. She reports that her mother was overweight and suffered from angina but had no history of diabetes.

Physical examination: Weight 198 lb (90 kg); height 5′4″ (162 cm); BMI 34.4; waist circumference 40.8″ (102 cm); BP 138/86 mmHg.

Laboratory investigations: FPG 11.4 mmol/L; A1C = 10% consistent with average glucose 15.5 mmol/L; urinalysis shows 2+ glucose, and otherwise negative (no protein, no nitrites, no leucocytes); uACR 3.6; TC 6.7 mmol/L; HDL 0.9 mmol/L; LDL 3.2 mmol/L; TC/HDL 7.4; Trig 3.8 mmol/L.

Ms M.J. has type 2 diabetes mellitus with obesity, the metabolic syndrome, diabetic nephropathy with microalbuminuria, and hypertension. The latter two diagnoses place her at high cardiovascular risk. She is advised that very low-calorie diets tend to be associated with cycles of weight loss and gain, but she is satisfied with her program and has lost 12 pounds over the past month.

Because her A1C is >9%, CDA guidelines suggest that we start her on two therapeutic agents. Because of her insulin resistance, we consider a TZD together with metformin, but she is opposed to this strategy because her weight loss support group has given her a list of medications to avoid, believing they may cause weight gain. Included on the list are TZDs, SUs and insulin. She is started on metformin (250 mg once a day, titrated up to 1000 mg twice daily). At the same time, she starts sitagliptin 100 mg once daily. She is also given the ARB losartan 100 mg once daily for hypertension and nephropathy, the goals being not only to achieve BP <130/80 mmHg but also to reduce the uACR to <2.5 mg/mmol. She is given a statin at a dose adequate to reduce LDL to <2 mmol/L (simvastatin 40 mg once a day).

FOLLOW-UP

She was seen in follow-up one week later: BP was down to 128/78 mmHg, and electrolytes and creatinine were normal. She had lost two more pounds and had been doing well with her exercise program. She returned three months later, having lost a further 10 lbs. FPG was 7.2 mmol/L and A1C was 7.9%, consistent with an average glucose of 11.3 mmol/L. As her weight loss progresses, we expect to see a further reduction in A1C. She is booked for follow-up and A1C testing in three months. If A1C has not significantly improved, we will add another agent. ●

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