



New Medications in Diabetes



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The term diabetes mellitus denotes a group of disorders that are clinically and genetically heterogeneous, but characterized by hyperglycemia. The latter is due to an abnormality of insulin secretion secondary to progressive dysfunction or apoptosis of beta cells; or resistance to insulin-mediated glucose uptake, or to a combination of these processes.

In Type 2 diabetes, in addition to hyperglycemia, there exists an insulin resistance syndrome or a cardiovascular dysmetabolic syndrome which is characterized by hypertension, hyperinsulinemia, dyslipidemia, central obesity, and a procoagulant state, all of which contribute

to the development of atherosclerosis manifested clinically by coronary artery disease, peripheral vascular disease, or cerebrovascular disease. This results in a two to fourfold increase in cardiovascular risk and a life expectancy that is 15 to 18 years less than nondiabetic patients.^{1,2}

Type 2 diabetes has become one of the major public health issues in North America and around the world. According to estimates, prevalence of diabetes mellitus is 130 million people worldwide, but by 2025, there will be 300 million individuals with diabetes mellitus. In North America 20 million people have diabetes, and this number is expected to triple by 2006.

Case

Mark, a 52-year-old accountant, presented with a three-month history of fatigue, blurring of vision, and frequency of micturition. He had a 30-pack/year history of smoking and was on no regular medications. Functional inquiry was unremarkable. His father also had Type 2 diabetes mellitus.

On examination, he was 175 cm tall, weighed 90 kg and had a body mass index of 29.4. Blood pressure was 150/90 mmHg, sitting. He had a right femoral bruit. Lab investigations revealed a pre-meal sugar of 16.4 mmol/L, 2 hour post-meal of 26.2 mmol/L, and HbA1c of 12%. Total cholesterol was 7.14 mmol/L, triglycerides 15.81 mmol/L, HDL of 0.62 mmol/L, and total cholesterol to HDL ratio of 11.51. The urinary albumin to creatinine ratio was 2.4 with a normal of 2.

Evidence-Based Management

Large scale clinical trials including the Diabetes Control and Complication Trial (DCCT), UK Prospective Diabetes Study (UKPDS), and Kumamoto in Type 1 and 2 diabetes have demonstrated that intensive treatment of hyperglycemia (*i.e.*, glycated hemoglobin A (HbA1c) less than 0.7, pre-meal blood sugar less than 7, post-meal blood sugar less than 7.8) results in significant reduction in microvascular complications and a trend towards reduction in macrovascular disease.^{3,4,5} For example, in

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UKPDS a 1% decrease in HbA1c was correlated with a 14% decrease in the risk of myocardial infarction.

In a meta analysis of 20 studies, dysglycemia of any degree was shown to be a continuous risk factor for the occurrence of a cardiovascular event and may require intervention in people with fasting blood sugars of greater than 5.5 or two-hour post-meal of greater than 7.8 mmol/L.⁶

Action to Control Cardiovascular Disease in diabetes (ACCORD) and the Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) are now evaluating the effect of attaining normal glycemia (HbA1c < 6%) among other interventions, on the occurrence of macrovascular complications in Type 2 diabetes mellitus.^{7,8}

Management of Type 2 diabetes should not simply be “gluco-centric” but include strategies to address the other components of the cardiovascular dysmetabolic syndrome including hypertension, dyslipidemia, obesity, atherosclerosis, and a procoagulant state. Both the UKPDS and Hypertensions Optimal Treatment Study (HOT) trial have underlined the need for aggressive management of hypertension, and current guidelines recommend a target blood pressure of less than 130/80 mmHg in those without nephropathy and 120/70 mmHg or less in those with nephropathy.⁹ angiotensin-converting enzyme (ACE) inhibitors are the agents of first choice. In the Losartan Intervention for Endpoint reduction in hyperten-

sion trial (LIFE), losartan, an angiotensin receptor blocker conferred a risk reduction of nearly 40% when compared to atenolol based treatment.¹⁰ A mean of three or even more agents has been found to be necessary to achieve these targets.

In a substudy of Heart Outcomes Prevention Evaluation trial (HOPE), 3,577 people with diabetes, aged 55 or older with one additional cardiovascular risk factor, were randomized to ramipril or placebo. Ramipril lowered the risk of combined primary outcome by 25%, myocardial infarction (MI) by 22%, stroke by 33%, and cardiovascular death by 37%. The cardiovascular benefit was greater than that attributable to modest decrease in the blood pressure.

In the Heart Protection Study, 3,982 diabetic patients with no previous history of congenital heart disease (CHD) were treated with 40 mg a day of simvastatin.¹¹ This resulted in a 28% reduction in major vascular events regardless of the baseline low-density lipoprotein level, underscoring the need for statin therapy in nearly all Type 2 diabetics.

In another study of secondary prevention (VA-HIT), in 627 men with Type 2 diabetes mellitus who were treated with genfibrozil, there was a 24% reduction in the death rate from CHD, stroke, or nonfatal MI.¹²

Enteric-coated ASA 81 mg or 325 mg should also be included to address the atherothrombotic risk unless there are contraindications to its use.

New Pharmacologic Approaches to Glycemic Control

Currently there are six classes of agents available in Canada for glycemic control. (Table 1) Another three look promising and should be available in the not too distant future.

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Metformin reduces hepatic glucose output by suppressing gluconeogenesis, enhances insulin-stimulated peripheral uptake of glucose and can also induce modest weight loss by suppressing appetite. In monotherapy, glucose was reduced by 2 mmol/L and HbA1c by 0.9% compared to placebo.¹³

Glimepiride is a third-generation sulfonylurea that is as effective as glyburide, but has a more rapid onset of action, shorter duration of endogenous insulin secretion and produces less hypoglycemia. It does not restore first-phase insulin release, but is more selective on the beta cell adenosine triphosphate dependent potassium (KATP) channel than on KATP channels in cardiovascular tissue. It may, therefore, have a favorable effect on ischemic preconditioning in the myocardium. It is administered orally once a day in doses ranging from 1 mg to 8 mg, and in clinical trials it reduces mean HbA1c by 1.2% to 1.9% and mean fasting plasma glucose by about 4.1 mmol/L.¹⁴

Nateglinide is a meglitinide analog and represents a new class of insulin secretagogues. It is a D-phenylalanine derivative and like repaglinide is absorbed rapidly, stimulates and enhances first phase insulin release, and is rapidly metabolized in the liver. It appears to lower postprandial glucose levels more than the sulfonylureas and is associated with less hypoglycemia. Reduction of HbA1c is equivalent, however, to sulfonylureas and Metformin when the latter are used as monotherapy. The recommended dose of nateglinide is 120 mg t.i.d. taken shortly before meals. In a study by Horton, 701 patients with type II diabetes mellitus were randomized to nateglinide 120 mg t.i.d. alone, metformin 500 mg t.i.d. alone, or a combination of nateglinide 120 mg and met-

Table 1

Hypoglycemic Agents

| Class | Examples |
|-----------------------------|-----------------------------------|
| Biguanides | metformin |
| Sulfonylureas | glyburide, glicazide, glimepiride |
| Meglitinides | repaglinide |
| Analogs | nateglinide |
| TZDs | pioglitazone, rosiglitazone |
| Alpha glucosidase inhibitor | acarbose |
| Insulin analogs | lispro, aspartate |

formin 500 mg t.i.d. after a period of washout. At the end of 24 weeks the HbA1c was reduced

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Discussion

Mark's Type 2 diabetes mellitus presents with several issues including glucose, lipid, blood pressure, and weight control. He likely has microalbuminuria which needs to be quantified, and an asymptomatic vasculopathy.

General principles of management would include lifestyle modifications, i.e., diet, exercise, smoking cessation, self-monitoring of blood glucose, and pharmacologic therapy with oral hypoglycemic agents. Metformin and/or thiazolidine (TZD) would be preferable as initial therapy followed by addition of sulfonylurea such as glimepiride or gliclazide. Nateglinide, rather than sulfonylurea, could also be considered, especially to target postprandial hyperglycemia. Further hypoglycemic therapy, including insulin, would depend upon his clinical response. Statin +/- a fibrate, ACE inhibitor, and acetylsalicylic acid are additional therapies that should be implemented as appropriate. Early and aggressive combination therapy should be part and parcel of the new paradigm.

by 1.4% in the combination group compared to 0.5% and 0.8% in the nateglinide and metformin groups, respectively.¹⁵ Fasting blood sugar was reduced by 2.4 versus 1.6 and 2.4 mmol/L, respectively.

Rosiglitazone and Pioglitazone - the thiazolidinediones (TZDs): The TZDs are insulin sensitizers. They enhance the sensitivity to insulin in adipose tissue, striated muscle, and to a lesser extent in the liver. They decrease hepatic glucose output and stimulate insulin mediated glucose uptake. Both agents are peroxisome proliferator-activated receptors (PPAR) gamma agonists, i.e., they bind to the nuclear receptor called PPAR gamma. These nuclear receptors act as central

transcriptional mediators in the regulation of different metabolic processes that influence adipogenesis, insulin sensitivity, glucose homeostasis, lipid metabolism, vascular endothelial function, atherosclerosis progression, and ultimately cardiovascular risk. TZDs take between 8 to 12 weeks to reach their maximum therapeutic effect, but lower levels of blood sugar are usually seen after two weeks. In monotherapy trials pioglitazone 45 mg once daily decreased HbA1c by up to 2.6% in oral hypoglycemic agents (OHA) naive patients.¹⁶ Fasting blood glucose was reduced by 4.4 mmol/L. Pioglitazone also had salutary effects on the lipid profile with decrease in triglycerides and increase in high-density lipoprotein levels. Peripheral edema has been reported in 5% to 15% of patients and tends to be more severe in combination with insulin and sulfonylurea as compared to monotherapy. It is contraindicated in patients with congestive heart failure or New York Heart Association Classification 3 or 4.

Glargine — a new long-acting insulin analog: Glargine insulin is a novel, long acting insulin created by substituting glycine at position 21 in the alpha chain and adding two arginines at position 30 in the beta chain of human insulin.¹⁷ This change in sequence results in more slow release from injection sites. Because insulin glargine does not have a peak, its profile appears more physiological than other basal insulins, and it has less potential for causing hypoglycemia. It can be used in conjunction with OHA as bedtime insulin or in place of normal-pressure hydrocephalus (NPH) in more intensive insulin regimes.

Protein Kinase C (PKC) inhibitors: Glucose uptake by vascular cells is largely insulin independent. Hyperglycemia per se may induce biochemical changes that cause physiologic vascular dysfunction and cellular disease. These biochemical changes have been shown to involve changes in the signal transduction pathways. The

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best studied effect of hyperglycemia on signal transduction pathways in vascular cells is represented by the PKC pathway. PKC is a cytoplasmic calcium-activated, phospholipid dependent kinase that acts as an intracellular signal transduction system for many cytokines and hormones. At least 11 isoforms of PKC have been identified at present.¹⁸ Hyperglycemia seems to result in an increase in diacylglycerol (DAG) which in turn activates PKC, which through activation of cytokines, cell permeability and vascular proliferation may induce atherosclerotic change. The synthesis and characterization of a specific inhibitor for PKC beta isoform, LY333531, has led to early animal trials, the results of which are promising. These results will need to be confirmed in humans.

Glucagon-like peptide 1 receptor agonists¹⁹ (GLP-1): The glucagon-like peptide receptor belongs to a distinct group of G protein coupled peptide hormone receptors. GLP-1 is an insulinotropic gut peptide that functions as an incretin and, when bound to the receptors, stimulates insulin secretion. Exendin 4 is a potent and long-acting agonist of GLP-1 receptor. In one study plasma insulin response was potentiated four to fivefold in both diabetics and nondiabetics. It will be some time before the exact role of GLP-1 receptor agonists in the treatment of diabetes is established in clinical practice.

Gene Therapy: Research into diverse avenues for gene therapy in diabetes mellitus are being pursued at present. Prevention of beta cell autoimmunity is a specific gene therapy for prevention of Type 2 diabetes mellitus in the preclinical stage, whereas improvement in insulin sensitivity of peripheral tissues is a specific gene therapy for Type 2 diabetes mellitus. Multiple approaches to insulin replacement by gene therapy include: stimulation of beta cell growth,

Table 3

Approaches to Gene Therapy

- Stimulation of beta cell growth
- Induction of beta cell differentiation regeneration
- Genetic engineering of non beta cells to produce insulin
- Transplantation of engineered islets or beta cells

Adapted from: Yamaoka-T: Gene therapy for diabetes. *Curr Mol Med* 2001; 1(3):325-37.

DEPOSITION OF QVAR



(n = 6 healthy volunteers)

Adapted from Leach et al.

QVAR is indicated for the prophylactic management of steroid-responsive bronchial asthma in patients who are 12 years or older. QVAR is not indicated for the relief of acute bronchospasm. The most common adverse events whether treatment related or not, were headache 17% (11%), pharyngitis 10% (5%), inhalation route effects 7% (4%) and skin and appendage 5% (2%). ()=placebo.

Open-label pilot study.

Leach et al. *Eur Respir J.* 1998;12:1346-1353.
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induction of beta cell differentiation and regeneration, genetic engineering of nonbeta cells to produce insulin, and transplantation of engineered islets or beta cells. Currently, however, there are many technical challenges in implementing these strategies.

Conclusion

Diabetes mellitus confers an enormous disease burden in those who are affected. Large scale clinical trials have added much to our ability to understand and mitigate the risks of this burden. Innovative strategies including new classes of drugs based on the understanding of the molecular mechanism of insulin action in normal and disease states will continue to enhance our ability to meet these challenges. Further understanding of the molecular mechanism of endothelial dysfunction may contribute significantly to our ability to address the increased cardiovascular risk associated with diabetes mellitus. [CME](#)

References

1. Haffner SM, Lehto S, Ronnamaa T, et al: Mortality from coronary heart disease in subjects with Type 2 diabetes and in nondiabetics with and without prior M.I. *New Engl J Med* 1998; 339(4):229-34.
2. Subodh V: The cardiovascular dysmetabolic syndrome of insulin resistance. *Clinical Focus, Cardiovascular disease in Type 2 diabetes*.
3. Diabetes Control and Complication Trial (DCCT). *New Engl J Med* 1993; 329:977-86.
4. UKPDS Group. *Lancet* 1998; 352:837-53.
5. Kumamoto. *Diabetes Care* 2000; 23:Supp. 2. B 21-29.
6. Coutinho M, Gerstein HC, Wang Y, et al: The relationship between glucose and incident cardiovascular events. *Diabetes Care* 1999; 22:233-40.
7. Action to control cardiovascular disease in diabetes (ACCORD). Study Protocol 2.
8. Duckworth WC, McCarren M, Abraiva C, VADT: Glucose control and cardiovascular complications. *Diabetes Care* 2001; 24(5):942-5.
9. Hansson L, Zanchetti A, Carruthers SG, et al: Effects of intensive BP lowering and low dose Aspirin in patients with hypertension: Principle results of the HOT trial. *Lancet* 1998; 351:1755-62.
10. Dahlof B, Devereux R, Devereux U, et al: Life Study Group. Losartan intervention for end point reduction in hypertension. *American Journal of Hypertension* 1997; 10:705-13.
11. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with Simvastatin in 20,536 high risk individuals. *Lancet* 2002; 360(9236):7-22.
12. Bloomfield Rubins H, Davenport J, Babikian V, et al: VA-HIT. Genfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. *New Engl J Med* 1999; 341:410-18.
13. Johansen K: Efficacy of Metformin in the treatment of NIDDM metanalysis. *Diabetes Care* 1999; 22(1): 33-7.
14. Rosenstark J, Samolse E, Muchnora DB, et al: Glimepiride: A new once daily sulphonylurea. A double blind placebo controlled study of NIDDM patients. *Diabetes Care* 1996; 19:1194-9.
15. Horton ES, Clinkingbeard C, Gatlin M, et al: Nateglinide alone and in combination with Metformin improves glycemic control by reducing mealtime glucose levels in Type 2 diabetes. *Diabetes Care* 2000; 23(11):1660-5.
16. Aronoff S, Rosenblatt S, Braithwaite S, et al: Pioglitazone Study Group, Pioglitazone Hydrochloride monotherapy improves glycemic control in the treatment of patients with Type 2 diabetes. *Diabetes Care* 2000; 23(11).
17. Heinemann L, Linkeschova R, Rave K, et al: Time action profile of the long acting insulin analog insulin Glargine in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000; 23:644-9.
18. Leroith, Taylor, Olefsky in *Diabetes Mellitus a Fundamental and Clinical Text*, Second edition. Lippincott, Williams, & Wilkins.
19. Egan JM, Clocquet AR, Elahi-Dariush: The insulinotropic effect of acute Exendin-4 administered to humans; comparison of nondiabetic state to Type 2 diabetes. *Journal of Clinical Endocrinology Metabolism* 2002; 87(3):1282-90.
20. Yamaoka-T: Gene Therapy for Diabetes. *Current Molecular Medicine* 2001; 1(3):325-37.
21. Hope Study Investigations: Effects of Ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus. *Lancet* 2000; 355: 253-59.