Developments in Glycemic Control—Will New Concepts Mean Improved Management of Diabetes?

a report by

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The prevalence of diabetes in Europe has been dramatically increasing since the early 1990s. It is estimated that in 2007, 53 million people have diabetes in Europe. Quantitively, Russia and Germany have the highest number of people with diabetes, with a combined figure of about 17 million. When the age group of 22–79 years is considered, in some European countries—such as Ukraine, Germany, and Russia—as much as 10% of the population is affected by diabetes.[1] The obvious consequence of the epidemic of type 2 diabetes is an increase in both macro- and micro-angiopathic complications. In 2000, the number of excess deaths due to diabetes was estimated to be 2.9 million worldwide (5.2% of all death). The excess death rate in particular concerns the age group from 30 to 75 years.[2]

Why Do We Need Good Metabolic Control?

There are a number of reasons to achieve good metabolic control. Intervention studies such as the Diabetes Control and Complications Trial (DCCT),[3] the UK Prospective Diabetes Study (UKPDS),[4] and the Steno II[5] studies have shown the importance of metabolic control in the prevention of diabetic complications. In addition, the large number of people with diabetes implies enormous health costs if prevention and control are not better achieved. However, long-term control is particularly difficult to achieve because diabetes is a disease in which compliance with treatment and lifestyle is imperative to achieve success. Furthermore, the disease evolves with a progressive loss of β-cell function. Also, the available medications have limitations in terms of efficacy and side effects.

Treatment of Type 2 Diabetes—The New Guidelines

The standard approach to the management of type 2 diabetes is well accepted and simple in theory. At the time of diagnosis, diet, exercise, and monotherapy with metformin are widely accepted. When this therapy becomes insufficient, combination therapy with two or three oral agents is started. Later—when necessary—insulin is added to other therapies, and finally multiple injections of insulin have to be started for a significant percentage of diabetic patients later in the evolution of the disease. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) established recommendations for the treatment of type 2 diabetes in 2006.[6] Once the diagnosis of diabetes is established, these recommendations propose starting active lifestyle interventions plus metformin.

When these initial measures fail to maintain a glycated hemoglobin (HbA_{1c}) level under 7%, the recommendations are to add insulin, which is the most effective (at least acutely), a sulfonylurea (the least expensive), or a glitazone, which has the advantage of not causing hypoglycemia. When the second step is unable to maintain the HbA_{1c} level at less than 7%, additional combination therapy is required until intensive insulin treatment is started. Of note, metformin is maintained throughout these different steps. The different antidiabetic medications have similar efficacy, at least during the first year of treatment, and lead to decreases in HbA_{1c} of 1–2%. However, each has advantages and disadvantages (see *Figure 1*).

Lifestyle changes are low-cost and have many health benefits. Unfortunately, they are usually effective only in the short term because compliance is difficult to maintain. Metformin is weight-neutral and inexpensive; however, it has gastrointestinal side effects with rare episodes of lactic acidosis. Sulfonylureas are inexpensive too, but they cause weight gain and hypoglycemia. Glitazones markedly improve insulin resistance and triglycerides, but they are associated with fluid retention, weight gain, macular edema, and osteoporosis, and they are also expensive. Finally, insulin has no dose limits, is inexpensive, and leads to an improved lipid profile; however, it requires injections and can cause hypoglycemia and weight gain. Additional treatments such as glinides—which increase insulin secretion similar to sulfonylureas, but with a shorter duration of action—and alpha glucosidase inhibitors—which delay intestinal carbohydrate absorption—may be helpful in the treatment of diabetes, but usually have slightly decreased efficacy compared with the alternative treatments.

Treatments on the market include glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors, which improve glucose-dependent insulin secretion and lead to weight loss for the GLP-1 analogs.[7] These treatments are based on the observation that enteral nutrition provides a more potent insulinotropic stimulus compared with a comparable glucose intravenous load leading to the incretin concept. The two incretins identified in the last decade are GLP-1 and glucose-dependent insulinotropic peptide (GIP).[7] The first GLP-1 analog to enter the market is exenatide. Exenatide is a subcutaneously injected incretin mimetic. It is indicated as adjunctive therapy to improve glycemic control in patients who are already receiving therapy with metformin, a sulfonylurea, or both, and who have sub-optimal glycemic control. Exenatide improves glucose homeostasis by

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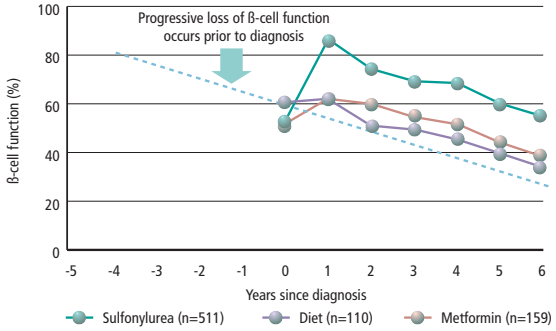
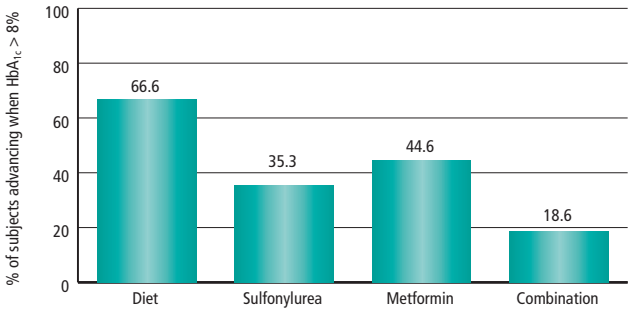
Figure 1: β-cell Function Continues to Decline Regardless of Intervention in Type 2 Diabetes Mellitus



β–cell function is measured by the homeostasis model assessment (HOMA).
Adapted from the UK Prospective Diabetes Study Group, 1995.[16]

Figure 2: Clinical Inertia



At insulin initiation, the average patient had five years with glycated hemoglobin (HbA_{1C}) >8% and 10 years with HbA_{1C} >7%.
Adapted from Brown et al., 2004.[17]

mimicking the actions of GLP-1. It improves glycemic control through an increase in glucose-dependent insulin secretion, partial restoration of first-phase insulin response, decreased glucagon secretion, delayed gastric emptying, and decreased food intake. In phase III trials, the addition to the usual treatment of exenatide 10µg twice a day resulted in a decrease in HbA_{1c} values of 0.8–1%. There was also dose-dependent progressive weight loss compared with placebo. Nausea was the most commonly reported adverse event in the exenatide groups (about 40%). Other adverse events occurring in more than 10% of patients receiving exenatide were hypoglycemia, diarrhea, and vomiting. Of interest, the reduction in HbA_{1c} was sustained over two years, as was the mean weight loss of about 5kg.[8]

A multinational, randomized, open-label study compared the effects of exenatide with insulin glargine in patients with type 2 diabetes who did not achieve adequate glycemic control with a combination of metformin and a sulfonylurea at maximally effective doses. At the end of 26 weeks of therapy, HbA_{1c} was decreased by 1.1% in both groups. However, mean bodyweight decreased by 2.3kg in the exenatide group and increased by 1.8kg in the insulin glargine group. Nausea was the most common adverse event in the exenatide group compared with the insulin glargine group, while the overall rate of hypoglycemia was similar in the two groups.[9] Anti-exenatide antibodies are detected in about 40% of patients treated in clinical trials. The majority of these patients have low antibody titers and no effects on glycemic control. Since exenatide delays gastric emptying, it may also affect the rapidity of absorption of multiple drugs.[8] Exenatide is a promising new treatment for type 2 diabetes, particularly when slow-release exenatide becomes available, allowing ease of use, weight loss, and improved glycemic control.

Liraglutide is the second GLP-1 agonist in development, and one of its qualities is as a free fatty acid addition to lysine 26. The acyl moiety promotes non-covalent binding to albumin, with 1–2% of liraglutide circulating possessing a non-albumin-bound free peptide. Liraglutide has a longer half-life compared with exenatide and can be given as a once-daily injection. So far, the efficacy and side effects of liraglutide are similar to those of exenatide.[7]

GPL-1 is normally rapidly degraded by DPP-4, a ubiquitous membrane-spanning cell-surface amino peptidase widely expressed in many tissues. The extra-cellular domain of DPP-4 can be cleaved from its membrane-anchored form and circulate in plasma, where it retains its full enzymatic activity. Many gastrointestinal hormones, neuropeptides, cytokines, and chemokines are substrates for DPP-4, among them both GIP and GLP-1, which are the hormones of the two incretins. On this basis, substances that inhibit DPP-4 have been designed. They specifically and potently inhibit the enzyme DPP-4 after oral administration. DPP-4 inhibitors have many of the actions observed with GLP-1 analogs, including stimulation of insulin and inhibition of glucagon secretion, preservation of β-cell mass through stimulation of cell proliferation, and inhibition of apoptosis, although these effects have not been demonstrated in humans. In contrast, DPP-4 inhibitors are not associated with delayed gastric emptying or weight loss.[7]

DPP-4 inhibition is accompanied by a rise in post-prandial levels of intact GLP-1 and GIP. Most studies published so far have been performed with either vildagliptine or sitagliptine. These substances are well tolerated and used as monotherapy or in combination with metformin or glitazones. Their efficacy on glycemic control is similar to that of metformin, sulfonylureas, or glitazones, and they are weight-neutral.[7] No major adverse events have been associated with the use of DPP-4 inhibitors, despite the large number of potential substrates for DPP-4. However, the long-term safety profile of DPP-4 inhibitors is still unclear. For instance, the use of 100mg as a single dose of vildagliptine has resulted in increased liver function tests in a small percentage of patients; furthermore, a slight increase in upper respiratory tract infections has been observed with these agents. Overall, agents that enhance incretin actions show great promise for the treatment of type 2 diabetes, with favorable effects, not only on glycemic control but also on weight and potentially on β-cell function in the context of a currently favorable safety profile. However, long-term clinical studies are needed to better assess the role and true benefits of these drugs.

Endocannabinoid receptor antagonists such as rimonabant are also helpful in the treatment of type 2 diabetes due to their favorable effects on weight through inhibition of food intake and increased lipolysis.[10] The endocannabinoid system, which is functional in multiple organs including the brain, the adipose tissue, the liver, and the pancreatic β-cells, is overactive in obesity, probably secondary to a high-fat diet and increased food intake. This creates a vicious cycle, with increased lipogenesis in adipocytes and the liver leading to abdominal obesity and liver steatosis and, potentially, to excessive insulin secretion.[11] Thus, constant activation of the endocannabinoid system may play an important role in the pathophysiology of the metabolic syndrome. Therefore, cannabinoid receptor type 1 (CB1) receptor antagonists have multiple actions by blocking the effects of endogenous endocannabinoid on

different organs including anorexigenic effects through the hypothalamus, a decrease in motivation for palatable food through the nucleus accumbens, stimulation of anorectic signals through the gastrointestinal tract and glucose uptake by the muscles, and inhibition of lipogenesis in the liver and adipose tissue. The hypothetical benefits of CB1 receptor antagonists have generated an ambitious clinical program to study their effects in patients. Among the multiple studies, some were performed specifically in diabetic patients, including Rimonabant In Obesity (RIO)-diabetes and the Study Evaluating Rimonabant Efficacy in Drug Naive Diabetic Patients (SERENADE).[10,12] In both studies, a decrease of 5–6kg accompanied by a decrease of 5–6cm in waist circumference as well as 0.6–0.7% in the HbA_{1c} level was observed after six to 12 months. Unfortunately, these favorable effects on glycemic control and weight were accompanied by some serious adverse events, such as depressed mood, anxiety, irritability, insomnia, and suicidal ideas. Thus, depression appears as a formal contraindication to such treatment, and since depression is a common problem in obese patients the use of CB1-receptor antagonists may be limited at present. The full long-term safety profile of these agents needs to be better assessed.

Overall, these new treatments have similar efficacy with respect to the HbA_{1c} level compared with the older ones, their main advantage being the low frequency of hypoglycemia and their effects on weight. Their respective place in the algorithm for the treatment of type 2 diabetic patients will have to be further defined. It is clear that diabetes is one of the most difficult diseases to treat in the long term. Indeed, the UKPDS[4] and A Diabetes Outcome Progression Trial (ADOPT)[13] have shown that the HbA_{1c} level—which is invariably improved by any standard treatment at the beginning of the disease—often increases after two years of therapy, indicating that combination therapy is mandatory with time in most diabetic patients. Indeed, after nine years of follow-up in the UKPDS, only 11% of patients were still on diet, 21% on sulfonylureas, and 13% on metformin.

Unfortunately, while it is thought that control of diabetes should improve with the availability of more treatments, in fact this is not the case. The US epidemiological National Health and Nutrition Examination Survey (NHANES) revealed that between 1988 and 1994, 44.3% of the diabetic patients had an HbA_{1c} level of less than 7%, while a more recent study performed between 1999 and 2000 revealed that this number had actually decreased to 37%, illustrating that despite more evidence in favor of metabolic control to prevent complications and the availability of more treatment modalities, diabetes treatment remains a difficult task.[14] For instance, in the STENO II study the percentage of patients reaching an HbA_{1c} level of less than 6.5% was about 3% with conventional therapy and only 15% with intensive therapy.[5] Similar results were observed in Switzerland in five university centers. Indeed, an observational study reported that only 13% of patients treated in the diabetes clinics in these university hospitals had HbA_{1c} levels less than 6.5%.[15]

Table 1: Factors Limiting Use of Insulin in Type 2 Diabetes Mellitus

Need for specific materials (needle fear)
Need for specific teaching
Need for more rigorous diet obligations
Need for more frequent blood glucose monitoring
Psychosocial representation of disease severity
Hypoglycemia
Weight gain
Errors more likely

Why Do We Have So Much Difficulty Controlling Diabetes?

The progressive loss of β-cell function that is already ongoing at diagnosis of diabetes,[12] then the subsequent lifestyle changes even when patients are intensively educated (see *Figure 2*), are not always totally effective, as suggested by the STENO II study.[5] Also, many of the treatment options in diabetes lead to increases in weight, and these may have detrimental effects in the long term. Doctors should also react much earlier in trying to improve diabetes control in their patients. An elegant study showed that at insulin initiation, the average diabetic patient has spent about five years with an HbA_{1c} level of more than 8% and about 10 years with a level of more than 7%.[17] Multiple difficulties exist in adapting treatment, particularly starting insulin (see *Table 1*). Physicians always hope that lifestyle will eventually improve diabetes control. Patients are often reluctant to take more medications. For insulin, the need for education and the time spent demonstrating the use of specific materials and how to perform injections are major limiting factors. The requirements for more rigorous diet obligations and more frequent blood glucose monitoring, the appearance of more severe and more frequent hypoglycemia, the problem of weight gain, the risk of more errors, and a bad social representation of disease severity are all barriers to starting insulin. This requires good communication skills and time to convince patients that it will be beneficial for them. Although increases in medication or in prescribing insulin may be translated as an increase in disease severity, increased organisation, and more risks, this will eventually pay off with a decreased complication rate and an increased life span for the patient.

In conclusion, the major difficulties in controlling diabetes are mainly due to psychosocial reasons because of the daily requirements for self-management and compliance, the evolution of the disease, and the limitations of the available medications. Thus, new concepts may not mean improved management of diabetes. Improved management of diabetes will require more efforts from both the patient and the doctor. These efforts involve mandatory lifestyle adaptations and increased physician vigor to adapt treatment. However, the development of new treatments may offer major advantages in terms of diabetes control, because we need medications that lead to weight loss, and improved glucose and lipid profiles with good tolerance, limited side effects, and, eventually, improved life quality and expectancy. ■

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