

Treating Type 2 Diabetes with Respect

Until recently, type 2 diabetes mellitus received little respect from clinicians or patients, especially compared with its sibling, type 1 diabetes. Type 1 diabetes—characterized by onset at a young age, dramatic presentation, and acute metabolic emergencies (such as ketoacidosis)—has commanded our attention since its description more than 2000 years ago. Moreover, celebrity spokespersons have raised public awareness of this disease. Much basic and clinical diabetes research has focused on the pathophysiology and treatment of type 1 diabetes. This has resulted in the discovery and use of insulin, development of glucose monitoring devices, and the means of replacing deficient insulin secretion in a physiologic pattern with multiple daily injections and external and implantable pumps. In contrast, clear appreciation of a form of diabetes distinct from the “juvenile-onset” form did not emerge until the mid-1930s (1). The “adult-onset” form has often been treated dismissively as a mild form of diabetes that does not cause the litany of severe complications associated with type 1 diabetes.

We have finally awakened to the fact that type 2 diabetes, whose very designation suggests second-class citizenship, is actually the predominant form of diabetes and is a major public health problem in the United States and elsewhere. Epidemiologic surveys reveal that type 2 diabetes is one of the most common chronic severe diseases in the world, affecting an estimated 12% of the adult population aged 40 to 74 years in the United States (2). Moreover, the clinical characteristics of type 2 diabetes belie any suggestion that it is mild. As the increased human life span results in longer exposure to type 2 diabetes, all of the complications that occur in type 1 diabetes are increasingly being seen in type 2 diabetes. Type 2 diabetes is a major cause of kidney disease, vision loss, and amputation in most countries in which its prevalence exceeds 5% (3).

Type 2 diabetes differs from type 1 in several fundamental ways. In addition to causing retinopathy, nephropathy, and neuropathy and their attendant long-term clinical sequelae, type 2 diabetes is accompanied by a twofold to fivefold increase in

the occurrence of macrovascular disease (4). Most patients with type 2 diabetes are obese and have hypertension, dyslipidemia, and cardiovascular disease; cardiovascular disease accounts for as much as 75% of all mortality among patients with type 2 diabetes (5).

Given the magnitude of the public health problem created by this highly prevalent disease, identification of the most beneficial therapies for type 2 diabetes should be high priority. The pathophysiology of type 2 diabetes—insulin resistance compounded by failing insulin secretion—lends itself to many therapeutic strategies. Insulin resistance can be decreased with diet, weight loss, and exercise or with medications, and insulin levels can be increased with agents that increase endogenous insulin secretion or with insulin injections (6). However, until recently, neither the appropriate metabolic goals of therapy nor the most advantageous therapy or combinations of therapies to achieve those goals had been clearly defined.

The United Kingdom Prospective Diabetes Study (UKPDS) (7, 8)—a large, long-term, multicenter clinical trial—and the article in this issue by Yki-Järvinen and colleagues (9) have begun to shed light on these issues. The UKPDS, which ended in 1998 after 20 years, was directed at determining whether intensive therapies aimed at bringing glyce-mic control as close to the normal range as possible would affect the long-term outcome of persons with newly diagnosed type 2 diabetes. In addition, the UKPDS compared different intensive therapies to determine which of the available agents was most likely to be beneficial. Although the UKPDS found an affirmative answer to the first question, demonstrating a clear benefit with regard to microvascular outcomes (but not for macrovascular outcomes), it did not provide a clear answer to help clinicians choose among therapy with insulin, sulfonylurea, or metformin. The failure of the UKPDS to determine which therapies were most advantageous was predicated, in part, on the design of the study, which allowed intensive interventions to be added over time and resulted in a substantial crossover of therapies (10). The results of the UKPDS with regard to the importance of intensive therapy reinforced

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the results from the Diabetes Control and Complications Trial (11), in which intensive therapy was demonstrated to have a major salutary effect on microvascular and neurologic complications in type 1 diabetes.

Results of the randomized trial by Yki-Järvinen and colleagues suggest that for patients in whom sulfonylurea therapy has failed to reduce their glycemic levels, combining insulin with metformin is advantageous compared with other combinations of oral agents and insulin or to insulin given twice daily. Combining insulin with metformin resulted in lower hemoglobin A_{1c} levels with less weight gain and fewer episodes of symptomatic hypoglycemia. Patients adjusted their own bedtime insulin dose on the basis of fasting glucose levels. Patients who received metformin adjusted their insulin doses more aggressively, using 50% more bedtime insulin than the other treatment groups. It is difficult to explain why patients who received metformin, who were blinded to their oral agent assignment, increased their insulin doses more aggressively. However, the higher dose of bedtime insulin in this group may explain the relative benefit of this combination with regard to decreased fasting blood glucose and hemoglobin A_{1c} levels compared with the other treatment groups. The authors suggest that lower frequency of hypoglycemic reactions and biochemical hypoglycemia may explain the willingness or ability of the patients treated with metformin and insulin to increase their insulin dose. Considering the infrequent occurrence and mild nature of these episodes—no patient experienced hypoglycemia that required medical assistance—this explanation is not convincing. On the other hand, the weight gain experienced by the other treatment groups may have inhibited them from increasing their insulin dose. The observation that metformin therapy is associated with less weight gain and less frequent hypoglycemia than sulfonylurea or insulin therapy is not new; it has been seen in other studies of monotherapy and combination therapy (7, 8, 12).

Whether the use of combined insulin and metformin will spare patients with type 2 diabetes the seemingly inexorable worsening of metabolic control that occurs over time, an effect that was observed in the UKPDS (7, 8), remains to be shown. In addition, combination therapy is more expensive than larger doses of insulin, which have been demonstrated in previous studies to result in near-normal glycemia with few, if any, episodes of severe hypoglycemia (13). Whether the added expense of com-

bination therapy is worth its weight-sparing effect is also open to question. Microvascular complications were decreased with intensive therapy in the UKPDS in the setting of weight gain (mean of 3.1 kg over 10 years), suggesting that the modest weight gain that accompanies nonmetformin intensive therapy is not overly pernicious. However, it is not known whether this degree of weight gain adversely affects macrovascular outcomes.

The study by Yki-Järvinen and colleagues adds to the accumulating data supporting the idea that intensive therapy goals can be achieved in type 2 diabetes with relatively low risk for hypoglycemia or weight gain. More aggressive efforts to lower glycemia will provide significant benefit with regard to long-term complications. Laissez-faire therapy for type 2 diabetes is no longer acceptable.

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References

1. **Himsworth HP.** Diabetes mellitus: its differentiation into insulin-sensitive and insulin insensitive types. *Lancet.* 1936;1:117-21.
2. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1998;21 Suppl 1:S5-S19.
3. **Nathan DM.** Long-term complications of diabetes mellitus. *N Engl J Med.* 1993;328:1676-85.
4. **Kannel WB, McGee DL.** Diabetes and cardiovascular disease. The Framingham Study. *JAMA.* 1979;241:2035-8.
5. **Panzram G.** Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia.* 1987;30:123-31.
6. **Dagogo-Jack S, Santiago JV.** Pathophysiology of type 2 diabetes and modes of action of therapeutic interventions. *Arch Intern Med.* 1997;157:1802-17.
7. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-53.
8. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:854-65.
9. **Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M.** Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med.* 1999;130:389-96.
10. **Nathan DM.** Some answers, more controversy, from UKPDS. United Kingdom Prospective Diabetes Study. *Lancet.* 1998;352:832-3.
11. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977-86.
12. **Cusi K, DeFronzo RA.** Metformin: a review of its metabolic effects. *Diabetes Reviews.* 1998;6:89-131.
13. **Edelman SV, Henry RR.** Insulin therapy for normalizing glycosylated hemoglobin in type II diabetes. *Diabetes Reviews.* 1995;3:308-34.

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