Glycemic control and complications of diabetes mellitus: practical implications of the Diabetes Control and Complications Trial (DCCT)

THE OBSERVATION that rigorous glycemic control reduces the risk for microvascular complications in diabetic animals has been well established for nearly two decades. Short-term studies have provided suggestive evidence that the same might be true for microvascular and neuropathic complications in humans with diabetes mellitus.[1] Furthermore, the concept that glucose itself might be the culprit has been suggested by several observations. First, the complications are essentially the same in all types of diabetes mellitus, irrespective of the pathophysiologic mechanism of hyperglycemia. Second, glycation of proteins may damage structural tissues and thus contribute to the risk for microvascular and macrovascular damage. Third, sorbitol, an alcohol formed from glucose, may accumulate when glucose levels exceed those generally necessary for oxidation as a source of energy in the body. Such sorbitol accumulation in tissue may affect the metabolic machinery.

The Diabetes Control and Complications Trial (DCCT), a prospective, randomized, multicenter clinical study, was conceived in the early 1980s to address the question whether rigorous glycemic control would lessen the risk for development and progression of diabetic complications.[2–4] Three key components in the management of diabetes mellitus permitted such a clinical trial to be undertaken: improved insulin preparations (both human and purer animal insulin preparations), assays for integrated measures of glycemic control such as glycated hemoglobins (eg, HbgA1c), and fingerstick glucose tests that could be performed by patients.

The recently published results of the DCCT[5] have important implications for the management of diabetes mellitus. We will summarize the key features of the study and the recommendations of the investigators, review issues of implementing intensive management of diabetes mellitus, and emphasize what it means for the primary care physician. Finally, the difficulties with implementation cannot be satisfactorily addressed without some attention to what methods will be used in the future to try to achieve normal or near-normal glycemic control.

THE DESIGN AND THE RESULTS

The DCCT investigators recruited 1441 patients aged 13 through 39 with type I diabetes. The primary outcome measured was retinopathy, determined by graded photography of the fundus. Other outcomes measured included nephropathy (reflected by albuminuria and renal function), neuropathy (determined by clinical evaluation, electromyography and autonomic testing), and atherosclerotic disease (determined clinically).

The study had a primary prevention arm (comprising patients with no retinopathy at baseline) and a secondary prevention arm (comprising patients with very early retinopathy at baseline). Approximately half the patients in each arm were randomly assigned to undertake intensive glycemic control. The target HgbA1c level for this group was 6.05% (2 standard deviations above the mean for a nondiabetic control group), and the target glucose level was 70 to 120 mg/dL in the preprandial state, <

180 mg/dL after meals, and > 65 mg/dL at 3 AM. The actual HgbA1c level achieved by this group was about 7% for the duration (mean follow-up 6.5 years) of the clinical trial.

The other patients received treatment similar to typical outpatient management of diabetes mellitus, with less intensive monitoring and less frequent insulin injections. A ceiling HbgA1c level of 13% was set, and the group achieved a value of about 9% for the duration of the trial.

With intensive glucose control there was approximately a 50% reduction in the risk for onset and progression of diabetic retinopathy (*Table*). There was a similar reduction in risk for onset and progression of diabetic nephropathy as determined by the presence of microalbuminuria (≥ 40 mg/24 hours) or dipstick-positive albuminuria (≥ 300 mg/24 hours). The incidence of diabetic neuropathy was also reduced by about 50%. The reduction of risk for retinopathy was continuous as a function of the HgbA1c level and did not demonstrate any threshold effect. In any year, an average of 1% of patients who had an HgbA1c level of 5.5% experienced onset or progression of retinopathy; this rate increased to a mean of more than 8% at HgbA1c levels of over 10%. The benefits of improved glycemic control were much greater than many diabetologists expected.

The benefits of intensive glucose control, however, were not achieved without some adverse effects. The most significant problem was a threefold increase in the risk for severe insulin reactions in the intensive treatment group. This problem occurred most commonly in patients who had difficulty detecting insulin reactions. Intensive glycemic control was also accompanied by weight gain, especially in adolescent women—a factor that had a demonstrable impact on tempering enthusiasm for "tight" control.

The patients had to have a very high degree of commitment: they monitored their glucose levels four or more times a day, gave themselves multiple insulin injections, and tailored their diet and exercise regimens to maximize blood glucose control. The study used a labor-intensive approach by a team that included nurses, physicians, dietitians, and behaviorists. The commitment of time and energy, the cost, and the expertise necessary to achieve tight control all have implications for the implementation of the conclusions of this trial into clinical practice.

TABLE
REDUCTION OF RISK FOR APPEARANCE OR PROGRESSION OF DIABETIC COMPLICATIONS WITH INTENSIVE GLYCEMIC CONTROL*

Complication	Risk reduction, %	95% Confidence interval
Appearance of retinopathy (primary prevention)	76	62–85
Progression of retinopathy (secondary prevention)	54	39–66
Urinary albumin excretion (mg/24 hours)		
≥40	39	21–52
≥300	54	19–74
Clinical neuropathy at 5 years†	60	38–74

*Data from reference 5
†Excluding patients with clinical neuropathy at baseline

THE NEED FOR INTENSIVE INSULIN THERAPY

The difficulty in achieving near-normal glycemia is directly related to the fact that subcutaneous insulin therapy is a poor substitute for endogenous insulin secretion. The pancreas is exquisitely sensitive to carbohydrate and protein levels; in response to nutrient intake, it secretes insulin in a biphasic fashion directly into the portal system, where half is cleared by the liver in the first pass. In contrast, insulin administered subcutaneously is absorbed erratically over a prolonged time, and dose adjustment only crudely approximates insulin needs as they change with nutrient intake or exercise. Moreover, insulin is usually given peripherally rather than into the portal system, thus depriving the liver of adequate quantities to optimize glucose regulation.

One of the lessons of the DCCT is the need to adjust insulin schedules to conform to the patient's life-style, taking into account variability in eating[6] and activity patterns. This is in sharp contrast to the more traditional approach of prescribing a regimen of insulin and diet and hoping that the patient will be able to adapt to it. Tailoring a regimen of insulin, diet, and exercise for each patient is labor-intensive but necessary to achieve near-normal glycemia. The difficulties of intensive therapy were acknowledged by the DCCT investigators in their summary paragraph:

"Intensive therapy was successfully carried out in the present trial by an *expert team* [italics added] of

diabetologists, nurses, dietitians, and behavioral specialists, and the time, effort, and cost required were considerable. Because the resources needed are not widely available, new strategies are needed to adapt methods of intensive treatment for use in the general community at less cost and effort. Meanwhile, the health care system should provide the support necessary to make intensive therapy available to those patients who will benefit."

APPLYING THE RESULTS: PRACTICAL MATTERS

Most patients with type I diabetes receive their care from primary care physicians and allied health personnel in the physician's office. What should be the role of primary care physicians in managing type I diabetes mellitus?

We would suggest that, first, physicians make their patients aware of the results of this study and the significant effect that intensive glycemic control may have on reducing the risk for microvascular and neuropathic (and perhaps atherosclerotic) complications.

Second, they need to help make available to such patients the resources necessary to achieve intensive control. Patients need instruction in measuring their glucose levels and adjusting their insulin dosages according to their glucose level, food intake, and activity level,[6] and they need to have their HgbA1c levels monitored. Above all, they need time, understanding, and encouragement from physicians and other health care professionals. For physicians who are comfortable with multiple-dose insulin therapy but do not have office resources that include experienced nurse educators or nutritionists, there are an increasing number of such allied health professionals who work on a consulting basis. Physicians who are not comfortable initiating and maintaining such therapy may need to refer some of their patients to teams with experience in intensive management.

A somewhat unsettling report by Tuttleman et al[7] indicated that many primary care physicians acknowledge the importance of achieving near-normal glycemia and concur with the need for frequent glucose monitoring and insulin injections, but fewer than half of such physicians actively implement these recommendations. The DCCT results give new impetus for practice to conform more closely to expressed beliefs.

Convincing reluctant patients

Obviously, some patients who would benefit from intensive therapy are hesitant to initiate it, for very understandable reasons. In our experience, some patients are quite vocal about their reluctance or frustration with the effort required to maintain near-normal glycemia. Intensive therapy with multiple fingerstick glucose determinations and insulin injections does interfere with many daily activities. The costs of visits to some members of the team, such as dietitians, may not always be covered by third-party carriers. The same holds true in many cases for the expenses associated with capillary glucose monitoring supplies. The increased risk of hypoglycemia, which may interfere with driving (and even jeopardize a driver's license) or daily activities at work or home are unacceptable to some patients.

Some of these objections can be addressed by pointing out that improvement in glycemic control is likely to confer benefit even if near-normal glycemia cannot be achieved. The risks for hypoglycemia are correspondingly less with higher HgbA1c levels. A gradual approach to lowering glucose levels may be more successful than intensifying control rapidly in reluctant patients. Abruptly improving glycemic control in patients who have had poor control for a long time may paradoxically cause an increase in diabetic retinopathy, at least temporarily.[8,9] In fact, the patients in the secondary prevention arm of the DCCT who underwent intensive treatment had a higher incidence of progression of retinopathy during the first year than did patients treated conventionally, and the benefit of intensive treatment did not become apparent until 36 months.[5]

Extrapolating the results

The issue of whether these results are broadly applicable to all patients with diabetes mellitus, especially those with type II diabetes, is not entirely resolved. In all probability, the mechanisms for the microvascular and neuropathic complications are the same as in type I diabetes mellitus, and improved glycemic control should reduce the risk for these complications. However, the burgeoning literature on possible adverse effects of hyperinsulinemia and associated obesity on the risks for macrovascular complications suggest that the risks of intensive therapy may be different in insulin-resistant type II diabetes mellitus.

Trials currently underway may resolve these is-

sues satisfactorily.[10] Whether the results are generally applicable to patients younger than age 13 with type I diabetes is also uncertain. Since the complications "clock" may not start ticking until puberty, glycemic control that permits normal growth and development is advisable, but near-normal glycemia cannot be uniformly recommended in all children at present.

WHERE DO WE GO FROM HERE?

The DCCT results provide new impetus to find better ways to achieve near-normal glycemia. A number of studies are currently examining insulin analogs that have absorption characteristics which appear to be more rapid and reproducible than currently available insulins. There has been clear progress in animal studies of islet xenografts encapsulated in porous microspheres or microtubules which preclude the need for immunosuppressive therapy. If stable materials can be found to encapsulate porcine islets—a logical and potentially unlimited source of islets—then the transplantation of such islets into type I diabetic subjects may render many of the problems noted above obsolete.

In the meantime we need to provide type I diabetic patients with the information and tools to help them reduce the risk for the complications that may tangibly interfere with both quality and length of life.

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