Toward Risk Factor Control for all Patients With Diabetes

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Twenty years after insulin use for diabetes mellitus began, a debate was joined over the intensity of blood glucose control and the prevention or reversal of vascular complications (1,2). "Control the blood glucose well and you will avoid complications," advised one school of thought. Others countered that vascular complications were "fellow travelers," intrinsic to diabetes, probably related to the genetic makeup of the diabetic person, and unrelated to the degree of blood glucose control. The latter view was supported by the clinical observation that some patients with diabetes failed to avoid retinopathy and nephropathy, despite "a diabetic lifetime of good control," whereas other patients were noted to be singularly free of serious complications, despite little effort to optimize blood glucose levels. Over the years, a slow accumulation of retrospective data has supported the view that the better the blood glucose control, the fewer and milder the microvascular complications.

Final answers to this polemic remain elusive. The advance in the application of insulin therapy and the ability to self-monitor the blood glucose accurately and to measure glycosylated hemoglobin with precision have prompted prospective clinical trials that investigate the relationship between the intensity of blood glucose control and the appearance or advance in vascular complications. Studies of this nature are prodigious undertakings that require money, investigator time, detailed protocols, sophisticated clinical skills, and a dedication by patients and investigators alike that dwarf the demands of previous trials.

These clinical trials address the need to answer the debate of the past 50 yr. Will blood glucose control prevent or ameliorate vascular complications? If so, how intense must that control be? Will long-term morbidity and mortality be altered by intense blood glucose control? Do the risks of intensive control overshadow the benefits? These questions have been addressed by recent clinical trials involving patients with IDDM. Many of the earlier trials were short term, involved small numbers of patients, and were mainly interventional. They tested feasibility. Their reports suggested that near-normal glucose control lessened retinopathy and microalbuminuria. Effects on macrovascular disease, important as it is to the morbidity and mortality of the diabetic patient, have been more difficult to study because of imprecise end points, the long duration of IDDM before macrovascular disease is apparent, and the difficulty in assessing what influences these end points. Younger IDDM patients have been preferred for study, for the date of onset of their clinical disease is more easily identified and the likelihood of coexisting disease is usually absent.

The protocol for the DCCT recruited patients with IDDM who were either free of microvascular disease or in whom the manifestations were minimal (3). This prospective, randomized clinical trial is now in its 10th yr, and plans to report its data by mid-decade. The major end points of eye and kidney microvascular disease and their correlation to the intensity of blood glucose control should permit a definitive statement on what to advise patients with IDDM to prevent or modify microvascular disease. Issues in the 50-yr debate on the effect of glycemic control on microvascular disease should be clarified by this report. Clinicians, who advise diabetic patients, will be able to transfer data from the DCCT report so as to enhance the medical outcomes of their patients.

But what of the large body of diabetic patients who have NIDDM? Are data from a study on IDDM patients transferrable to those with NIDDM? Purists would say no; the pragmatists (mostly clinicians who will advise these patients) will feel obliged to apply guidelines of therapy for microvascular disease garnered from the DCCT to those in their care with NIDDM if no parallel study on NIDDM exists. Therefore, a study involving NIDDM patients would bolster the comfort of the pragmatists and strengthen the science of diabetes management to the pleasure of the purists. Resolution of this uncertainty by a successful NIDDM study is appropriate inasmuch as clinical diabetes is sufficiently heterogeneous that application of data end points from a trial focused on IDDM patients to patients with NIDDM seems derivative. A protocol for a NIDDM study is presented by Abraira et al. (this issue, p. 1572–80) who outline

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; DCCT, DIABETES CONTROL AND COMPLICATIONS TRIAL; VACSDM, DEPARTMENT OF VETERANS ADMINISTRATION COOPERATIVE STUDY ON GLYCEMIC CONTROL AND COMPLICATIONS IN NIDDM.

the design of a multicenter, feasibility trial on whether two degrees of intensity of blood glucose control can be achieved in NIDDM patients.

The Department of Veterans Administration Cooperative Study on Glycemic Control and Complications in NIDDM (VACSDM) is as exciting as was the DCCT in 1982. The investigators have properly taken a page from the DCCT, and, although the DCCT protocol is not mimicked, VACSDM draws on its strengths. In many ways, this trial will be more challenging than the DCCT, for patients with NIDDM are older, will have varying intensities of insulin resistance and β-cell dysfunction, and may enter the study with more established vascular disease, as well as with disorders unrelated to diabetes. Although the DCCT volunteers were free of obvious macrovascular problems at entry, this will not be so for the recruits in the VACSDM. Indeed, a primary end point of the main study is to assess the effect on cardiovascular disease of two degrees of intensity of blood glucose control. This question, a critically important one in diabetes management, is not addressed by the DCCT.

Some thoughts about the VACSDM naturally arise out of experience in the DCCT. Cardiovascular events are affected by several nondiabetic factors (i.e., hypertension, cigarette smoking, serum cholesterol levels, family history) that make the interpretation of the influence of blood glucose control more arbitrary. It is easier to identify a cause and effect relationship between blood glucose control and diabetic microvascular disease than when one deals with cardiovascular events. It may be difficult to assign a reason why a patient manifests a cardiovascular end point. A modest statistical difference between treatment arms, if present, is less influential when the cause of the morbid state is considered multifactorial. A large, randomized study should vitiate this problem.

It will be imperative to include women in the long-term study. The duration of the study may be longer than predicted if cardiovascular events are fewer than expected. The broader range of glucose intolerance in NIDDM patients, varying from minimal hyperglycemia to severe insulin resistance, could alter predictable responses to insulin therapy. Although one might expect the goal of euglycemia to be more easily achieved in VACSDM than DCCT patients, diet compliance and insulin insensitivity may make the goals of therapy in the intensively controlled arm of VACSDM as elusive as it is in the experimental arm of the DCCT. The VACSDM protocol should permit early intensification of blood glucose control. One can envision the entire period of the feasibility study consumed by adjustments in therapy short of a goal. An aggressive approach in the experimental arm is advisable; use of oral sulfonylureas should be optional. The important therapeutic end point is intensified blood glucose control, not the means to achieve it. Proper patient selection for dedication to the study and the willingness to adhere to a prescribed diet (the Achilles heel in many diabetes studies) is paramount in VACSDM, for without a dedicated patient, self-empowered for the protocol and being a key member of the research team, the study may flounder and the results will be inconclusive. In achieving the goals of the protocol, no factor in the DCCT has superseded a dedicated patient linked to a dedicated research team.

Diabetologists will follow VACSDM with interest. If the feasibility trial is successfully completed, a full-scale study should follow. Such a trial would permit the accumulation of data in the NIDDM patient on intensity of glucose control and its effect on vascular complications. The VACSDM along with the UK Prospective Diabetes Study (4,5), which is designed to compare the efficacy of diet, oral agents, and insulin on glycemic regulation in newly diagnosed NIDDM patients, will permit clinicians access to data from two sources on the management of NIDDM. Both IDDM and NIDDM will be with us for some time, despite the remarkable advances in the basic knowledge of diabetes that have been recorded recently by the research community. Though these advances are important links in the "knowledge chain" about diabetes, in themselves they offer little to the clinician at this time.

However, if the clinician understands the appropriate degree of blood glucose control required to achieve risk factor control for diabetic patients, with either IDDM or NIDDM, a giant step forward in management will have been accomplished. The best palliative care comes when practitioners achieve, based on scientific evidence, the optimal treatment goals for their patients. Although symptomatic therapy for diabetes has been the only goal for most patients over the past 70 yr, it is now time to rank risk factor control as a partner equal to symptomatic control. With an honest disagreement extant for >50 yr among clinical investigators about the degree of blood glucose control needed to prevent vascular complications, no clear recommendations on goals of therapy have been offerred to clinicians. Now it should be possible to do so; first for the microvascular complications in the IDDM patient as a result of the DCCT, and in time, for macrovascular complications for the NIDDM patient from the VACSDM. Both trials, successfully conducted, will bring reason to blood glucose control and vascular complications. Though these successful trials might squash the lively debate that has been the lifeblood of clinical sessions in diabetes circles for >50 yr, there is no reason to believe that other issues of keen interest will not take their place in center court. These issues should include the earlier identification of the NIDDM patient; this would permit initiation of risk factor control before manifest vascular complications. Too often now, therapy is interventional rather than preventive.

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