Implications of the Diabetes Control and Complications Trial

AMERICAN DIABETES ASSOCIATION

The DCCT is a landmark multicenter trial designed to test the proposition that the complications of diabetes mellitus are related to elevation of the plasma glucose concentration. The study design was simple. Two groups of patients were followed long term, one treated conventionally (goal: clinical well-being; called standard treatment group) and another treated intensively (goal: normalization of blood glucose; called intensive treatment group). The intensive treatment group was clearly distinguished from the standard treatment group in terms of glycated hemoglobin levels and capillary blood glucose values throughout the duration of the study. Normalization of glucose values was not achieved in the intensively treated cohort as a group because mean glucose values were ~40% above normal limits. Nonetheless, over the study period, which averaged 7 years, there was an ~60% reduction in risk between the intensive treatment group and the standard treatment group in diabetic retinopathy, nephropathy, and neuropathy. The benefit of intensive therapy resulted in a delay in the onset and a major slowing of the progression of these three complications. Finally, the benefits of intensive therapy were seen in all categories of subjects regardless of age, sex, or duration of diabetes.

The American Diabetes Association believes that the study has both statistical and clinical significance. The DCCT is the longest and largest prospective study showing that lowering blood glucose concentration slows or prevents the development of diabetic complications. As such, it has major therapeutic implications for health-care providers and their patients. Many questions remain to be answered, but the following conclusions appear warranted:

1. A primary treatment goal in IDDM should be blood glucose control at least equal to that achieved in the intensively treated cohort. This goal may not apply to all patients with IDDM and must be based on clinical judgment. Of importance, intensively treated patients had a three-fold greater risk of hypoglycemia than did patients in the control group. Because serious hypoglycemia is dangerous, "tight" control goals may have to be sacrificed in people in whom frequent or severe hypoglycemia cannot be avoided by treatment modification.
2. It is not known for certain whether the results obtained in this study of people with IDDM apply to people with NIDDM. Nonetheless, it seems reasonable to recommend tight control in many patients with non-insulin-dependent disease because it is presumed that the mechanisms by which glucose causes complications is the same in both forms of diabetes. However, because there may be other medical conditions in people with NIDDM, tight control may not be appropriate for all people with this type of diabetes.
3. There is no favored form of treatment to achieve tight control of blood glucose levels. The decision to use multiple injections of insulin versus an insulin pump depends on the preference of the patient with IDDM and the ability of the health-care team to provide the necessary resources and support. In NIDDM, diet, exercise, and oral drugs may achieve tight control, but insulin is often required.

To expand on these conclusions, a list of pertinent questions and answers is provided.

DEFINITIONS

1. **IDDM.** This form of diabetes commonly develops in people <30 yr of age, which was the study group in the DCCT. Insulin is required in all patients, and its omission results in life-threatening diabetic ketoacidosis (diabetic coma). It is also called type I diabetes.
2. **NIDDM.** By far the most common form of diabetes, NIDDM usually begins in middle age but can occur earlier or later. It is called non-insulin-dependent to indicate resistance to diabetic ketoacidosis. Patients may be treated by diet or oral drugs (sulfonylureas), but many are best managed by insulin. NIDDM is also called type II diabetes.
3. **Complications.** Diabetes of both types may result in tissue-damaging complications. One set of complications is designated *microvascular*. Microvascular means small blood vessel, but this is simply traditional terminology and does not imply that the complications are *due* to blood vessel disease. The microvascular complications affect three organ systems: the eyes (ret-

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DCCT, Diabetes Control and Complications Trial; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

inopathy), the kidneys (nephropathy), and the nerves (neuropathy). These complications lead to visual loss, kidney failure, and multiple neurological symptoms (e.g., pain, burning, loss of sensation) in some patients. The purpose of the DCCT was to test the hypothesis that these complications could be prevented or their progress slowed by better control of blood glucose levels. *Macrovascular* means large blood vessel. Macrovascular complications are due to atherosclerosis of blood vessels, which results in reduced blood flow to tissues. Complications include angina, heart attacks, strokes, and amputations. In addition to hyperglycemia, other factors are important in the pathogenesis of atherosclerosis in diabetes. These include known risk factors in people without diabetes, such as smoking, high blood pressure, and abnormal blood lipid levels.

4. **Tight control.** This term is used to indicate blood glucose levels equal to or better than those achieved in the intensively treated group in the DCCT trial.
5. **HbA_{1c} or glycated hemoglobin.** This is a form of hemoglobin (the oxygen-carrying molecule of the blood) that reflects the average blood glucose concentration over a three-month period. A high percentage of HbA_{1c} indicates poor control, whereas a low percentage indicates good control.

THE AMERICAN DIABETES ASSOCIATION RESPONSE TO THE DCCT

1. **Are the results of the DCCT significant and reliable?** The DCCT was well designed and efficiently carried out. The results are statistically significant and are of major clinical importance. They convincingly demonstrate that blood glucose control significantly influences development of complications in subjects with IDDM. The study does not appear to have major flaws. As in all clinical trials, not every variable could be studied. In the DCCT, the age range of the study subjects was rather narrow and relatively few minority patients participated, but there is no reason to believe that the results would not apply to all people with IDDM.
2. **What level of glucose control should be sought?** It appears that there is a direct relationship between blood glucose level and the risk of complications. However, there are other factors, such as genetics, that influence complications. Nevertheless, patients should aim for the best level of glucose control they can achieve without placing themselves at undue risk for hypoglycemia or other hazards associated with tight control (see question 3). As has always been the case, therapy for diabetes must be individualized in consultation between patient and primary health-care provider. If the IDDM patient is intellectually, emotionally, physically, and financially able to attempt tight control, and if a health-care team is available to provide resources, guidance, and support, a reasonable goal is the mean plasma glucose and HbA_{1c} levels achieved in the intensive treatment group of the trial (i.e., mean blood glucose of 155 mg/dl and HbA_{1c} of ~7.2%; normal average blood glucose is ~110 mg/dl and HbA_{1c} is ≤6.05%).
3. **Is tight control of blood glucose dangerous?** It can be. The major danger is hypoglycemia. Serious hypoglycemia may result in altered consciousness, coma, or convulsions resulting in injury to the patient or others. Hypoglycemia may also have harmful effects on neuropsychological and intellectual function in children, although in DCCT participants, these adverse effects were not observed. In older people, low blood glucose may lead to strokes or heart attacks. The intensive treatment group in the DCCT had a threefold greater risk of severe hypoglycemia than did the standard treatment group.

   The risk of hypoglycemia must be recognized, although the danger may be reduced by frequent blood glucose monitoring; adjustment of insulin dosage; alteration of the timing, frequency, and content of meals; and change in exercise/activity patterns. Thus, comprehensive self-management training is essential.

   The intensive treatment group also experienced significant weight gain, which can have adverse medical and emotional consequences.
4. **Do the results of the DCCT apply to people with NIDDM?** Patients with NIDDM were not studied in the DCCT. However, there is no reason to believe that the effects of better control of blood glucose levels would not apply to people with NIDDM. The eye, kidney, and nerve abnormalities appear quite similar in IDDM and NIDDM, and it is likely that the same or similar underlying mechanisms of disease apply.

   Universal recommendations for tight control may not be appropriate, however. The weight gain characteristic of intensive therapy may be greater in subjects with NIDDM because a high percentage are overweight or frankly obese. Because obesity is associated with resistance to insulin action, a vicious circle of insulin administration → weight gain → increased insulin requirement is possible. Some investigators believe that the higher insulin concentrations required to overcome insulin resistance may be a factor in development of high blood pressure, abnormal lipid levels, and atherosclerosis in NIDDM. Also, because of an increased prevalence of macrovascular dis-

ease, older patients with NIDDM may be more vulnerable to serious consequences of hypoglycemia, including fainting, seizures, falls, stroke, silent ischemia, heart attack, or sudden death. Thus, as is the case for everyone having diabetes, treatment in NIDDM has to be individualized. But the results of the DCCT suggest that many otherwise healthy patients with NIDDM should strive to achieve tight control. Advanced age or significant comorbidity (e.g., cerebrovascular or coronary artery disease) should be considered a relative contraindication to tight control in NIDDM. Also, other factors important in the development of atherosclerosis in these patients, including smoking, elevated blood pressure, abnormal lipid values, and obesity, must be addressed.

5. **Is tight control contraindicated in any group of patients?** Tight control should not be attempted by patients unable or unwilling to participate actively in their glucose management. Tight control is contraindicated in infants less than 2 years old. It should be undertaken with extreme caution in children between the ages of 2 and 7 years because hypoglycemia may impair normal brain development, which is not complete until 7 years of age. The danger of hypoglycemia is greater in infants and children because food intake, activity, and adherence to treatment schedules are less predictable than in adults. Because preadolescents appear to be relatively protected from microvascular complications, the need for tight control might be less than in postpubertal subjects. Older patients with significant atherosclerosis may be vulnerable to permanent injury from hypoglycemia. Although there are few absolute contraindications to tight control, relative contraindications will be more frequent. Clinical judgment and common sense will be required in decision making under the latter circumstance. Given the above caveats, multiple insulin injections and frequent blood glucose monitoring from the onset of IDDM should be standard therapy.
6. **Should tight control be the goal of therapy for patients with established complications?** Again, clinical judgment is required. Unless patients have advanced, severe complications, the answer would often be yes. Tight control may not be indicated for patients who already have marked visual loss or end-stage renal disease. Patients with advanced complications were not entered into the trial, so no direct evidence is available to indicate that tight control in such patients in beneficial.
7. **Should intensive therapy be offered to patients with long-standing diabetes and no evidence of microvascular complications?** If a person has had diabetes for 20–25 years following puberty without signs of retinal, nerve, or kidney disease or if complications are minimal (e.g., one or two microaneurysms in the retina), tight control might not be necessary.
8. **Will tight control prevent macrovascular complications?** Atherosclerosis occurs earlier in people with diabetes than it does in those without elevated blood glucose levels, and it is reasonable to suppose that better control might slow macrovascular in addition to microvascular complications.
9. **Is there any way to predict genetic susceptibility to diabetic complications?** As was mentioned earlier, susceptibility to complications and damage from elevated blood glucose levels is influenced by one's genes. Unfortunately, we have not identified markers of susceptibility.
10. **For those choosing tight control, is life-long intensive treatment required?** In general, tight control for people beyond puberty should be maintained for life. Alteration of therapy may be required because of advanced age or other changes in clinical circumstances; e.g., after a stroke or heart attack, signaling more serious risks from hypoglycemia.
11. **Are the results of the DCCT achievable for most people with diabetes?** In theory, the answer is yes. However, in the real world, great effort will be required to reproduce the results of the DCCT. It must be recognized that the study group was young, generally healthy, and highly motivated. The professional personnel conducting the study were trained endocrinologists and diabetes educators in academic centers who were highly motivated and meticulous in their management of the study subjects. The intensively treated group received far more attention and medical services than are routinely available in clinical practice. In many cases, participants and professionals became "family." Broad implementation of intensive therapy will require expanded health-care teams (knowledgeable physicians, diabetes educators, nutritionists, and social workers), major professional and patient educational efforts, and an enhanced partnership between specialists and primary care providers. The costs of these services and reimbursement mechanisms will have to be addressed (see question 13).
12. **What form of intensive treatment is recommended?** Improved glucose control in IDDM had beneficial effects whether delivered by multiple daily injections or programmable insulin-infusion pumps. The choice of treatment depends on the wishes of the individual patient and the comfort/competence of the health-care team with a given technique.
13. **Will the postulated benefits of better control be worth the increased costs?** It is recognized that there will be substantially in-

creased costs of widely applying the recommendations of this study in the United States. There will also need to be additional efforts to ensure professional education, so that health practitioners are able to effectively and safely implement the therapy employed in the DCCT. It is hoped that the long-term benefits of healthier, more productive lives with fewer complications will offset the costs of tight control. This issue is being studied. Ultimately this will be a societal decision.