Implications of the Diabetes Control and Complications Trial

AMERICAN DIABETES ASSOCIATION

The Diabetes Control and Complications Trial (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 the standard treatment group) and another treated intensively (goal: normalization of blood glucose; called the 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 type 1 diabetes 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 type 1 diabetes and must be based on clinical judgment. Of importance, intensively treated patients had a threefold greater risk of hypoglycemia than 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. The documented methods to achieve tight control in type 1 diabetes include multiple (three or more) daily injections or treatment with an insulin pump. The decision to use multiple injections of insulin versus an insulin pump depends on the preference of the patient with type 1 diabetes and the ability of the health care team to provide the necessary resources and support. In type 2 diabetes, medical nutrition therapy, exercise, and oral glucose-lowering drugs may achieve tight control, but insulin is often required.

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 type 1 diabetes. 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 type 1 diabetes.

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). Any improvement in blood glucose control has been shown to slow the development and progression of microvascular complications.

As has always been the case, therapy for diabetes must be individualized in consultation between patient and primary health care provider. If the type 1 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 [8.6 mmol/l] and HbA$_{1c}$ of ~7.2%; normal average blood glucose is ~110 mg/dl [6.1 mmol/l] and HbA$_{1c}$ is ≤6.05%).

3. **Is tight control of blood glucose dangerous?** It can be. The major danger is hypoglycemia, especially in people with type 1 diabetes. 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,

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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 the standard treatment group.

The risk of hypoglycemia must be taken into consideration, 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 type 2 diabetes?** Patients with type 2 diabetes were not studied in the DCCT. However, the largest and longest study on patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS), conclusively demonstrated that improved blood glucose control in these patients reduces the risk of developing retinopathy and nephropathy and possibly reduces neuropathy. The overall microvascular complications rate was decreased by 25% in patients receiving intensive therapy versus conventional therapy. Epidemiological analysis of the UKPDS data showed a continuous relationship between the risk of microvascular complications and glycemia, such that for every percentage point decrease in HbA_{1c} (e.g., 9 to 8%), there was a 35% reduction in the risk of microvascular complications. These results confirm in type 2 diabetes that lowering blood glucose is beneficial. The UKPDS also showed that aggressive control of blood pressure, consistent with American Diabetes Association recommendations, significantly reduced strokes, diabetes-related deaths, heart failure, microvascular complications, and visual loss.

Several observational studies, including the results of the epidemiologic analysis of UKPDS data, have shown strong and statistically significant associations between blood glucose control and the risk of cardiovascular disease morbidity and mortality. The UKPDS showed a 16% reduction (not statistically significant, $P = 0.052$) in the risk of combined fatal or nonfatal myocardial infarction and sudden death in the intensively treated group.

For further discussion, see the American Diabetes Association's position statement "Implications of the United Kingdom Prospective Diabetes Study."

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 <2 years of age. 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 type 1 diabetes 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 is beneficial.

7. **Should intensive therapy be offered to patients with long-standing diabetes and no evidence of microvas-** **cular 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. The DCCT was reassuring in demonstrating that there was no increase in cardiovascular disease in the setting of intensive therapy.

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 lifelong 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). Even if the DCCT results are not achieved, any improvement in blood glucose control has been shown to slow the development and progression of microvascular complications.

12. **What form of intensive treatment is recommended?** Improved glucose control in type 1 diabetes 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 increased costs of widely applying the recommendations of this study in the U.S. 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. The cost-benefit ratio for intensive therapy is in a range similar to other commonly accepted treatments in the U.S.

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