Blood Glucose Control and Microvascular and Macrovascular Complications in Diabetes

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High blood glucose levels for several years is the major factor in the development and progression of microvascular complications in IDDM. Reducing mean blood glucose reduces the risk of progression of diabetic microvascular complications substantially. A curve-linear relationship exists between HbA_{1c} levels and progression of diabetic retinopathy. Recent evidence also points to a close relationship between high blood glucose levels and progression of microvascular complications in NIDDM. The relationship between mean blood glucose and cardiovascular disease in diabetes has been unclear. Recent population-based studies give evidence for a linear association of glycemic control with the risk for cardiovascular disease in patients with NIDDM. However, randomized studies comparing different degrees of glycemic control in NIDDM and their impact on cardiovascular morbidity and mortality are urgently needed. *Diabetes* 46 (Suppl. 2):S101–S103, 1997

MICROVASCULAR COMPLICATIONS IN IDDM

Tight blood glucose control is of great value in avoiding or delaying the onset and progression of diabetic retinopathy, nephropathy, and neuropathy in IDDM. In the decade before the Stockholm study and the Diabetes Control and Complications Trial (DCCT), a number of prospective clinical trials supported the notion that blood glucose control was very important to delaying microvascular complications in IDDM patients (1). A careful meta-analysis (2) of a number of smaller, mostly European studies showed that intensive insulin treatment compared with control insulin treatment (with a mean reduction in HbA_{1c} of 1.4% during the study period) reduced the risk of retinopathy and nephropathy progression (odds ratios 0.49 and 0.34, respectively). The only study addressing whether the development of microvascular complications can be prevented in IDDM patients is the DCCT (3). In the primary prevention cohort, intensive insulin treatment reduced the risk of developing sustained three-step progression of retinopathy by 76% compared with conventional treatment. In the patients who already had some retinopathy, intensified insulin treatment slowed the progression of retinopathy by 54% and reduced the development of proliferative or severe nonproliferative retinopathy by 47%. In the two cohorts combined, intensive treatment reduced the occurrence of microalbuminuria (urinary albumin excretion >40 mg/24 h) by 39%, that of macroalbuminuria by 54%, and that of clinical neuropathy by 60%.

After the DCCT, no doubt should exist that intensified insulin treatment resulting in near-normal blood glucose levels substantially reduces the risk of microangiopathy. However, it is still debated what level of glycosylated hemoglobin should be the goal in IDDM and whether there exists a threshold for glycosylated hemoglobin below which the risk of microvascular complications is negligible.

The DCCT group states flatly in a recent analysis: "There does not appear to be a level of glycemia below which the risks of retinopathy progression are eliminated" (4).

This may be true for retinopathy, but the risk of development of microalbuminuria in the DCCT study increases substantially only when HbA_{1c} increases beyond approximately 8.8%, although this is not stated in the paper (5). These results are similar to those from the Joslin clinic (6) and the Stockholm study (7) showing that albumin excretion increases substantially when long-term HbA_{1c} is more than 8.8–9.0%.

If the goal is to avoid any signs of retinopathy (a few microaneurysms), normoglycemia may be necessary (3). However, the Stockholm study looked at the number of patients who developed serious retinopathy with the need for photocoagulation treatment and found that none developed serious retinopathy over the period of observation when long-term HbA_{1c} was less than 7.0% (7).

Quite recently, the DCCT study (7a) has reiterated that the risks of retinopathy progression and of developing microalbuminuria and neuropathy were found to be continuous but nonlinear over the entire range of glycosylated hemoglobin.

We might conclude that to be reasonably sure that a patient will not develop *any* microvascular complications, the treatment goal should be glycosylated hemoglobin within the normal range. However, if the clinical goal is to avoid serious microvascular complications, HbA_{1c} <7.0 will suffice, and any permanent reduction in HbA_{1c} will improve the prognosis regarding microangiopathy.

What then is the main determinant of progression of retinopathy? That is total glycemic exposure over time (4,8).

Does intensive insulin therapy as we know it today just delay or might it prevent microvascular complications? This is not known. Looking closely at the retinopathy data in the DCCT study, it is apparent that the treatment effect increases with time, perhaps suggesting that good glycemic control can reverse early microvascular complications (9). Recent data show that established microalbuminuria may be reversed with HbA_{1c} <7.0% (10).

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AGE, advanced glycation end product; DCCT, Diabetes Control and Complications Trial.

MICROVASCULAR COMPLICATIONS IN NIDDM

In most European countries and in the U.S., more than 90% of diabetic patients have NIDDM. Thus, from a public health point of view, the question of how important good blood glucose control is to the development of microvascular and macrovascular complications in NIDDM is a very important one for this group of patients (11).

As with IDDM patients, retrospective studies show a strong association between indexes of hyperglycemia and the prevalence of diabetic retinopathy, nephropathy, and neuropathy in NIDDM (14). The microvascular complications in NIDDM are very similar to IDDM both morphologically and clinically. They only develop in those diabetic patients who have long-standing hyperglycemia.

The 10-year results from the Wisconsin epidemiological study are interesting (12,14). They showed that some determinations of glycosylated hemoglobin predicted the incidence and progression of both nonproliferative and proliferative retinopathy 10 years later. Diabetic patients were divided into three groups: onset of diabetes before 30 years of age, onset after 30 years on insulin treatment, and onset after 30 years not on insulin treatment. Thus, the last two groups mostly had NIDDM. The patients were divided into quartiles according to glycosylated hemoglobin at baseline. The 10-year progression rate of retinopathy increased substantially from the lowest to the highest quartile of glycosylated hemoglobin, being more than 90% in the diabetic patients with the highest baseline quartile of glycosylated hemoglobin.

Even more impressive is that the progression to proliferative retinopathy is dependent on the level of glycosylated hemoglobin. In the lowest quartile of glycosylated hemoglobin in the older-onset, not-on-insulin group, the risk is 2%; it is 30% in the highest quartile. The authors conclude "these data suggest a beneficial effect in terms of lowered risk of progression of retinopathy in individuals with IDDM and NIDDM even in those with moderate to high hyperglycemia at baseline" (14).

However, we have lacked a DCCT-like trial comparing intensified and standard insulin treatment in NIDDM. The first trial of this type has been published from Japan (15). A total of 110 patients with NIDDM was randomly assigned to a multiple insulin injection treatment group (MIT group) or to a conventional insulin treatment group (CIT group). As in the DCCT, the Japanese study had a primary prevention cohort and a secondary intervention cohort. The cohorts were studied for a 6-year period. Intensified insulin treatment reduced both the development and the progression of diabetic retinopathy, nephropathy, and neuropathy.

The risk reduction in that study was of the same magnitude as that shown for IDDM in the DCCT study. Thus, there is every reason to believe that the main mechanism of microvascular complications in NIDDM is identical to that in IDDM, namely hyperglycemia.

However, we are increasingly recognizing the heterogeneous nature of NIDDM. The patients with NIDDM in the Japanese study were lean but not insulin deficient. On the other hand, about 8–9% of apparently NIDDM patients in many populations may actually turn out to have insulin-dependent diabetes, or latent autoimmune diabetes of adults (LADA). Thus, the propensity to hyperglycemia and hence to microvascular complications may vary substantially between the different types of NIDDM.

RISKS OF INTENSIFIED INSULIN TREATMENT

The most serious risk of intensified insulin treatment is severe hypoglycemia. The DCCT showed a threefold increment in severe hypoglycemia. However, there was no difference between the intensified and conventional treatment group in the occurrence of clinically important changes in neuropsychological function (3).

In the Japanese NIDDM study, hypoglycemia was not a major problem: six patients in the multiple insulin injection treatment group and four patients in the conventional insulin treatment group had one or more episodes of mild hypoglycemic reactions, but no patient experienced episodes of coma seizure or severe hypoglycemia that required the assistance of another person (15).

GLYCOSYLATED HEMOGLOBIN

Given the large predictive value of glycosylated hemoglobin determination for the development and progression of microvascular complications, a reliable method for this determination is mandatory. Unfortunately, no stable standard for HbA_{1c} exists, and numerous studies have shown unacceptable variations within and between laboratories (16). A joint effort to improve this situation is underway.

OTHER IMPORTANT FACTORS FOR THE DEVELOPMENT OF MICROVASCULAR COMPLICATIONS

Genetic factors seem to be important to the development of diabetic nephropathy, as even with very high mean blood glucose levels for several years, only 40% of IDDM patients will develop diabetic nephropathy. Family clustering of diabetic nephropathy has also been described (17). Genetic factors are probably not of major importance for the development and progression of retinopathy, as more than 90% of diabetic patients with poor glycemic control for many years will develop retinopathy. There is a preponderance of men among those with nephropathy and proliferative retinopathy.

MORTALITY AND HYPERGLYCEMIA

Is increasing hyperglycemia associated with increasing mortality in IDDM and NIDDM? In the Wisconsin study (13), the 10-year survival rate of older-onset diabetic patients in the quartile with the lowest hemoglobin was 62.8%; the rate declined to 41.7% in the highest quartile of glycosylated hemoglobin.

MACROVASCULAR DISEASE AND HYPERGLYCEMIA

In the DCCT, cardiovascular events were also reduced, albeit not significantly, by 41% in the intensively treated group. Several recent studies have shown a close correlation between quartiles of glycosylated hemoglobin and risk of developing cardiovascular disease (18,19). The risk of dying from cardiovascular disease was also associated with mean blood glucose in the Wisconsin study (14).

Obviously, this correlation does not necessary imply causality, and large-scale intervention studies like the DCCT are urgently needed to assess cardiovascular events in NIDDM. We welcome the initiative by the Veterans Administration Hospital to set up a large-scale intervention study in NIDDM (20,21). In the feasibility trial, the investigators were able to separate HbA_{1c} levels between intensive and standard insulin therapy by >2%. The pilot study suggested that intensive insulin therapy may be associated with an early

excess of cardiovascular events in this patient group, although the number of events were small. The single greatest predictor of such events, however, was a previous history of cardiovascular disease, and the insulin dose itself was not predictive (21).

The U.K. Prospective Diabetes Study was not structured to compare intensive glycemic regulation with insulin to standard insulin therapy, as was done in the DCCT. The study compares the effectiveness of diet, sulfonylurea, biguanides, and standard insulin therapy (not intensive insulin therapy) in controlling hyperglycemia from the discovery of NIDDM in the individual patient. Over nine years, the difference in HbA_{1c} between the intensive and conventional group was only 0.8% (22), making it perhaps difficult to observe differences in endpoints, whether these are micro- or macrovascular in nature.

The study showed that there is a progressive β-cell failure with duration of diabetes, making it necessary to switch a large number of patients to insulin treatment because they had unsatisfactory blood glucose control when treated with oral drugs. This is in line with the experience of others (23).

What is the mechanism for the deleterious effect of hyperglycemia of small and large blood vessels in diabetes? This is basically unknown, but recent studies suggest that modification of proteins by advanced glycosylation end products (AGEs) might play an important role (24). We have recently shown that measurement of serum AGE predicts the development of early morphological changes in human diabetic nephropathy (25).

WHAT SHOULD BE THE GOAL FOR GLYCEMIC CONTROL?

The goals should be individualized according to age and life expectancy. Recent data (12) suggest that the dose-response curve for retinopathy versus glycosylated hemoglobin is very similar for IDDM and NIDDM. So it will be prudent to strive for a glycosylated hemoglobin of <1.5% above the upper limit of normal in IDDM patients (26) as well in younger NIDDM patients with a long life expectancy. If this cannot be achieved with diet alone in NIDDM, a sulfonylurea should be used. However, the natural progression of hyperglycemia in NIDDM is faster than most doctors think, and insulin treatment will be necessary for many patients in the long run. This is in line with the recent consensus statement of the American Diabetes Association: "If glycemic goals [in NIDDM] are not achieved with combination therapy [with oral drugs] then treatment with insulin alone is indicated" (27).

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