Perspectives in Diabetes

Hyperglycemia and Cardiovascular Disease in Type 2 Diabetes

Markku Laakso

Cardiovascular disease (coronary heart disease, stroke, peripheral vascular disease) is the most important cause of mortality and morbidity among patients with type 2 diabetes. Conventional risk factors contribute similarly to macrovascular complications in patients with type 2 diabetes and nondiabetic subjects, and therefore, other explanations have been sought for enhanced atherothrombosis in type 2 diabetes. Among characteristics specific for type 2 diabetes, hyperglycemia has recently been a focus of keen research. A recent meta-analysis of 20 studies on nondiabetic subjects has demonstrated that in the nondiabetic range of glycaemia (<6.1 mmol/l), increased glucose is already associated with an increased risk for cardiovascular disease. Similarly, 12 recent prospective studies have convincingly indicated that hyperglycemia contributes to cardiovascular complications in patients with type 2 diabetes. The recently published U.K. Prospective Diabetes Study has shown that intensive glucose control reduces effectively microvascular complications among patients with type 2 diabetes, but that its effect on the prevention of cardiovascular complications was limited. Given the fact that in the U.K. Prospective Diabetes Study, none of the treatment modalities was particularly effective in reducing glucose, this underestimates the true potential of the correction of hyperglycaemia in the prevention of cardiovascular disease in type 2 diabetes. However, in addition to intensive therapy of hyperglycemia, other conventional risk factors should also be normalized to prevent cardiovascular disease in patients with type 2 diabetes.

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Type 2 diabetes is a common disease affecting ~3-5% of people living in Western countries. Cardiovascular disease accounts for ~70% of total mortality, and all manifestations of cardiovascular disease, coronary heart disease (CHD), stroke, and peripheral vascular disease are substantially more common in patients with type 2 diabetes than in nondiabetic individuals (1-3). Most studies have indicated that this excess risk for macrovascular complications cannot be explained by abnormal levels of conventional cardiovascular risk factors. Therefore, the diabetes state itself, particularly hyperglycemia, is likely to contribute to excessive cardiovascular risk in patients with type 2 diabetes.

Diabetes is preceded by a long period of asymptomatic hyperglycemia. This prediabetic state (4) was first recognized in 1980 when the World Health Organization revised the diagnostic criteria for diabetes and impaired glucose tolerance (IGT), a category that falls between normal glucose tolerance and diabetes (5). In the prediabetic state, fasting blood glucose can be maintained at a near-normal range for years, whereas postprandial or postglucose levels are mildly elevated. In frank diabetes, multiple defects in insulin action and insulin secretion lead to hyperglycemia, and insulin’s effect on glucose uptake in skeletal muscle, glucose production in liver and kidneys, and lipolysis in adipose tissue is impaired, as well as the ability of glucose to stimulate insulin secretion (6). According to the current view, overt hyperglycemia develops when pancreatic β-cells fail to compensate for impairment in insulin action in peripheral tissues. Although this concept is likely to be an oversimplification, and is certainly not true in uncommon forms of insulin secretion defects in patients with maturity-onset diabetes of the young (MODY) (7), it offers a good model for research on determinants of cardiovascular disease before full-blown diabetes develops.

Several studies have indicated that cardiovascular complications are already frequent at the diagnosis of type 2 diabetes (1,2). In fact, subjects with IGT have about a twofold increase in the risk of macrovascular disease (1,2). Therefore, to understand the role of hyperglycemia in the pathophysiology of macrovascular disease in patients with type 2 diabetes, it is essential to also review literature on nondiabetic subjects. Pure epidemiological evidence is insufficient to verify causality between hyperglycemia and cardiovascular disease, and therefore mechanisms via which hyperglycemia could enhance atherothrombosis will be discussed. Finally, evidence is presented from clinical trials aiming to reduce the burden of cardiovascular disease by intensive glucose control.

Threshold of Glucose to Increase the Risk of Cardiovascular Complications: Does It Exist?

The first reports on glucose as a risk factor for cardiovascular complications were published in 1965 in the U.K. (the Bedford Study) (8) and the U.S. (the Tecumseh Study) (9).

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AGE, advanced glycosylation end product; CHD, coronary heart disease; IGT, impaired glucose tolerance; UGDP, University Group Diabetes Program; UKPDS, U.K. Prospective Diabetes Study.
These cross-sectional analyses suggested that elevation of glucose could be associated with CHD mortality, and indeed, follow-up data from these two cohorts verified this hypothesis. The first systematic and extensive evaluation of glucose as a risk factor of cardiovascular complications was published in 1979 by the International Collaborative Group based on 4–15 years of follow-up data from 11 different studies (10). The results were inconsistent, however, probably because of a short follow-up period, a small sample size in some of the studies, and a lesser degree of standardization of the oral glucose tolerance test. Therefore, the authors concluded that the 11 studies they evaluated did not show any consistent, strong, and graded association between asymptomatic hyperglycemia and CHD (10).

Coutinho et al. (11) have recently published a meta-regression analysis of 20 studies including 95,783 nondiabetic individuals who had 3,707 cardiovascular events and who were followed for 12.4 years. The authors applied the Poisson regression method to generate three mathematical models (linear, quadratic, exponential) describing the baseline glucose level and the relative risk of cardiovascular events for each study. The relative risk was defined as the ratio of cardiovascular event rate at a blood glucose concentration of 4.2 mmol/l (75 mg/dl), at which the relative risk was set to 1. The β-coefficients were calculated for all studies and β-coefficients were then combined for an overall β-coefficient for each glucose category.

Meta-analysis by Coutinho et al. (11) showed that high fasting, 1-h, and 2-h glucose values increased the risk for cardiovascular events, but that casual glucose did not (Fig. 1). The association of fasting glucose (β = 0.606 [95% CI 0.13–1.099], P = 0.016), based on six studies, and 2-h glucose (β = 0.531 [0.204–0.858], P = 0.0015), based on seven studies, with cardiovascular events was quite similar. Also, 1-h glucose, based on five studies, was significantly associated with cardiovascular events (β = 0.242 [0.084–0.400]). The exponential model provided the best fit for the combined data. Fasting glucose of 6.1 mmol/l increased the risk of cardiovascular events by 1.33 (1.06–1.67) compared with a fasting glucose of 4.2 mmol/l. Similarly, 2-h glucose of 7.8 mmol/l (140 mg/dl) was associated with a relative risk of cardiovascular events of 1.58 (1.19–2.10). When the data from the top glucose increment were omitted, there was still a significant relationship between 2-h glucose (P = 0.00064) and cardiovascular events, and almost a significant relationship between fasting glucose (P = 0.056) and cardiovascular events.

The study designs of the 20 different studies included in this meta-analysis were quite different: glucose was measured in blood, plasma, and serum and oral glucose tolerance tests were performed in different ways (from 50 to 100 g of glucose). Furthermore, a significant proportion of studies were excluded because they did not show the data in a form suitable for meta-analysis, and individual studies did not always give consistent results although the combined β-coefficient was positive. However, their analysis of the data from the Helsinki Policemen Study, the Paris Prospective Study, and the Whitehall Study yielded results similar to those recently published by Balkau et al. (12). Therefore, it is fair to conclude that glucose level seems to be a risk factor for cardiovascular events even within a range that is below the diabetic threshold. Glucose is likely to be a continuous cardiovascular risk factor, similar to total cholesterol and blood pressure.

**HYPERGLYCEMIA AND CARDIOVASCULAR RISK IN SUBJECTS WITH TYPE 2 DIABETES**

Although cardiovascular disease has been a focus of intensive research in patients with type 2 diabetes for decades, it is only in recent years that the role of hyperglycemia as a risk factor for cardiovascular disease has been clarified. Before the 1990s, hyperglycemia was not believed to contribute to cardiovascular disease in type 2 diabetes. This conclusion was based, however, on small studies and on scanty and inconsistent data (1,2).

Since 1993, several prospective studies including a large number of type 2 diabetic patients have shown that glycemic control is important for cardiovascular risk (13–24). These studies are summarized in Table 1. Only a few recent cross-sectional studies have not reported an association between glycemic control and cardiovascular complications (25).

The first study of this series to demonstrate a positive association between glycemic control and cardiovascular disease was published by Uusitupa et al. (13) in 1993 from Kuopio, eastern Finland. Among 133 middle-aged subjects with newly diagnosed type 2 diabetes, 10-year cardiovascular mortality increased threefold from tertiles of blood glucose and HbA1c. Hyperglycemia assessed at the time of diagnosis or at 5–10-year examinations was still a constant predictor for 15-year cardiovascular mortality (26). These observations were extended by Kuusiisto et al. (14,15) to older type 2 diabetic patients, aged from 65 to 74 years at baseline. HbA1c was a significant predictor not only for CHD events (14), but also for fatal or nonfatal stroke (15).

Several other studies from other European countries, but also from the U.S., have indicated that hyperglycemia is an important risk factor for cardiovascular disease. The San Antonio Heart Study demonstrated that hyperglycemia is a risk factor not only in Caucasians, but also in other ethnic groups (24). The Wisconsin Epidemiologic Study of Diabetic Retinopathy has systematically assessed the significance of glycemic control for micro- and macrovascular complications in 1,370 subjects with late-onset diabetes during 10 years of follow-up (17). A 1% increase in HbA1c resulted in a 70% increase in proliferative retinopathy and a 20% increase in proteinuria, but in only a 10% increase in CHD events. These results imply that hyperglycemia is likely to be a

![FIG. 1. Calculated regression coefficients for fasting, 1-h, 2-h, and casual glucose to increase the risk for cardiovascular events: meta-analysis of 20 studies (11).](image-url)
TABLE 1
Prospective studies showing an association between cardiovascular events and glycemic control in patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Length of follow-up (years)</th>
<th>End point</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>1993</td>
<td>133</td>
<td>45–64</td>
<td>10</td>
<td>Cardiovascular mortality</td>
<td>Uusitupa et al. (13)</td>
</tr>
<tr>
<td>Finland</td>
<td>1994</td>
<td>229</td>
<td>65–74</td>
<td>3.5</td>
<td>CHD mortality and morbidity</td>
<td>Kuusisto et al. (14)</td>
</tr>
<tr>
<td>Finland</td>
<td>1994</td>
<td>229</td>
<td>65–74</td>
<td>3.5</td>
<td>Stroke incidence</td>
<td>Kuusisto et al. (15)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1995</td>
<td>411</td>
<td>23–94</td>
<td>7</td>
<td>CHD mortality and morbidity</td>
<td>Andersson and Svärdssudd (16)</td>
</tr>
<tr>
<td>U.S.</td>
<td>1995</td>
<td>1,370</td>
<td>&gt;30</td>
<td>10</td>
<td>CHD mortality and stroke incidence</td>
<td>Klein (17)</td>
</tr>
<tr>
<td>Denmark</td>
<td>1995</td>
<td>328</td>
<td>20–65</td>
<td>5</td>
<td>Cardiovascular mortality</td>
<td>Gall et al. (18)</td>
</tr>
<tr>
<td>Germany</td>
<td>1996</td>
<td>1,139</td>
<td>30–55</td>
<td>11</td>
<td>Incidence of myocardial infarction</td>
<td>Hanefeld et al. (19)</td>
</tr>
<tr>
<td>Germany</td>
<td>1996</td>
<td>290</td>
<td>&lt;75</td>
<td>10</td>
<td>Cardiovascular mortality</td>
<td>Standl et al. (20)</td>
</tr>
<tr>
<td>Finland</td>
<td>1996</td>
<td>1,059</td>
<td>45–64</td>
<td>7</td>
<td>Stroke mortality and morbidity</td>
<td>Lehto et al. (21)</td>
</tr>
<tr>
<td>Finland</td>
<td>1997</td>
<td>1,059</td>
<td>45–64</td>
<td>7</td>
<td>CHD mortality and morbidity</td>
<td>Lehto et al. (22)</td>
</tr>
<tr>
<td>U.K.</td>
<td>1998</td>
<td>2,693</td>
<td>25–65</td>
<td>8</td>
<td>CHD mortality and morbidity</td>
<td>Turner et al. (23)</td>
</tr>
<tr>
<td>U.S.</td>
<td>1998</td>
<td>471</td>
<td>25–64</td>
<td>7.5</td>
<td>Cardiovascular mortality</td>
<td>Wei et al. (24)</td>
</tr>
</tbody>
</table>

The overwhelming evidence reviewed above indicates that hyperglycemia increases the risk for cardiovascular disease. The excess risk starts at levels of glycemia that are considerably lower than the threshold for the diagnosis of diabetes according to current diagnostic criteria.

A mild elevation of glucose either in the fasting state or postprandially could be a driving force for macrovascular complications. Hyperglycemia induces several harmful effects that could potentially contribute to atherothrombosis. High glucose is associated with increased oxidative stress (27), enhanced leukocyte-endothelial interaction (28), and glycosylation of virtually every protein in the body, including lipoproteins, apolipoproteins, and clotting factors. Over time, through a complex series of dehydration and oxidation reactions, the formation of advanced glycosylation end products (AGEs) occurs (29). AGEs can induce excessive cross-linking of collagen and other extracellular matrix proteins, particularly in the vascular wall, which could lead to the accumulation of LDL particles. Moreover, AGE-modified LDL has a prolonged half-life, which contributes to the oxidation of LDL particles (30). AGEs may also promote atherothrombosis through their effect on endothelial cell function (31). A recent study has indicated that treatment of diabetic mice deficient for apolipoprotein E with the soluble extracellular domain of the receptor for AGEs completely suppressed diabetic atherosclerosis (32). These findings suggest that AGEs and their receptor are involved in the development of accelerated atherosclerosis in the diabetic mouse model. Hyperglycemia can also increase sorbitol production via aldose reductase or alter signal transduction pathways. Limited information is available on hyperglycemia’s effect on signal transduction pathways, except for the activation of diacylglycerol and protein kinase C, which could be a common downstream mechanism by which multiple byproducts of glucose are exerting their adverse effects (33).

Good animal and in vitro models are not available to delineate mechanisms whereby hyperglycemia promotes atherothrombosis. Therefore, it is not clear how relevant in vitro experiments are for the understanding of the effects of hyperglycemia because the glucose range in these studies has often been from 5 to 20 mmol/L. At least these experiments cannot yield relevant results to explain why even a mild elevation of glucose is associated with a considerable increase in cardiovascular disease.

Another possibility to explain why subjects with mild hyperglycemia already have an excess of cardiovascular complications is the possibility that glucose itself is not causally associated with this risk, but is an innocent bystander, a component of the constellation of other risk factors potentially contributing to macrovascular complications. This kind of constellation is often seen in patients with Insulin Resistance Syndrome (Syndrome X) (34). Indeed, subjects having only a slight elevation of glucose often have hyperinsulinemia, elevated blood pressure, high total and VLDL triglycerides and small dense LDL, central obesity, and...
elevated levels of plasminogen activator inhibitor 1. Therefore, in the prediabetic state (including IGT) it is likely that the cluster of above-mentioned risk factors is more important for the risk of cardiovascular disease than is glucose level itself. However, this conclusion is likely to be restricted only to those prediabetic individuals with a considerable degree of insulin resistance (35). In contrast, prediabetic individuals who have diminished insulin secretion and who are insulin sensitive have quite a normal risk factor profile (35).

It has been suggested by Jarrett (36) and Stern (37) that type 2 diabetes (and the prediabetic state) and CHD could share common antecedents that could explain the strong association between them. This hypothesis is conceptually important, particularly for the prevention of cardiovascular disease in type 2 diabetes. If the hypothesis is right, the correction of one cardiovascular risk factor is surely not enough for the treatment or prevention of cardiovascular disease in type 2 diabetic patients.

TREATMENT OF HYPERGLYCEMIA: DOES IT REDUCE THE BURDEN OF CARDIOVASCULAR DISEASE?

Until now, information from clinical trials aiming to investigate the effect of the reduction of hyperglycemia on cardiovascular end points in type 2 diabetes has been very limited. However, clinical trials are needed to prove the causality between hyperglycemia and cardiovascular disease. Useful information has been available from type 1 diabetes, although we cannot be sure whether this information can be extrapolated to type 2 diabetic patients. The Diabetes Control and Complications Trial convincingly demonstrated that intensive insulin treatment of patients with type 1 diabetes reduced microvascular complications, but because of a low number of incident cases, intensive treatment did not significantly reduce cardiovascular events (38).

The first study aiming to investigate the treatment of hyperglycemia in type 2 diabetes was the University Group Diabetes Program (UGDP), which began in 1961 and was completed in 1975. This study randomized 619 patients to the following treatment regimens: placebo, phenformin, tolbutamide, a fixed insulin dose, and a variable insulin dose (39). Unfortunately, the UGDP did not solve the problem of how to treat hyperglycemia in type 2 diabetes. In contrast, it created a long-lasting debate and controversy. Patients treated with phenformin and tolbutamide had increased cardiovascular mortality, and therefore these study arms were stopped. The suspicion that oral agents are harmful in the treatment of patients with type 2 diabetes has persisted ever since. Insulin treatment groups and the placebo group had similar cardiovascular mortality (20.6 vs. 20.2%, respectively). Thus, the UGDP did not show any beneficial or harmful effects of insulin treatment.

Two other recent trials have yielded controversial results. The Veterans Affairs Cooperative Study in Glycemia Control, including 153 men with type 2 diabetes randomized to standard therapy or to intensive therapy, indicated that the CHD event rate was somewhat higher in the intensively treated group than in the conventionally treated group (21.3 vs. 11.5% NS) (40). In contrast, the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) trial, including 620 diabetic patients, showed that intensive insulin treatment was associated with a lower case fatality rate than placebo treatment in subjects with an acute myocardial infarction (18.6 vs. 26.1%, \( P = 0.03 \)) (41).

The most recent trial of all, the UKPDS, was published in September 1998 (42). This study, which was begun in 1977, was designed to investigate whether in 3,867 newly diagnosed patients with type 2 diabetes (median age 54 years), intensive blood glucose control could reduce the risk of macrovascular or microvascular complications, and whether any particular therapy was advantageous. Patients who after 3 months of diet treatment had a mean of two fasting plasma glucose concentration of 6.1–15.0 mmol/l were randomly assigned to an intensive policy with a sulfonylurea (chlorpropamide, glibenclamide, or gliptide) or insulin or to a conventional policy with diet. The treatment in general was not particularly successful because there was a linear increase in glucose levels with increasing duration of the trial even in intensively treated patients. Over 10 years, HbA1c was 7.9% in the conventional group and 7.0% in the intensively treated group—far from ideal glycemic control. The intensively treated group, as compared with the conventional treatment group, had a 12% reduction in any diabetes-related end point (microvascular and macrovascular complications), a 10% reduction in any diabetes-related death, a 6% reduction in all-cause mortality, a 16% reduction in myocardial infarction, and a 25% reduction in microvascular complications (retinopathy, nephropathy) (Table 2). Chlorpropamide, glibenclamide, and insulin similarly reduced diabetic complications.

### TABLE 2

<table>
<thead>
<tr>
<th>End point</th>
<th>Risk reduction (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related end point</td>
<td>12</td>
<td>0.03</td>
</tr>
<tr>
<td>Deaths related to diabetes</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16</td>
<td>0.05</td>
</tr>
<tr>
<td>Fatal</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke</td>
<td>11*</td>
<td>NS</td>
</tr>
<tr>
<td>Amputation or death from peripheral vascular disease</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>25</td>
<td>0.01</td>
</tr>
</tbody>
</table>

In statistical analysis of the data, 28 aggregate or single end points were included and no adjustment was made for multiple comparisons. *Increase in the risk.

### TABLE 3

Prevalence of hyperglycemia, elevated blood pressure, and high cholesterol and their risk reduction with intensive treatment for different end points

<table>
<thead>
<tr>
<th>Condition present (%)</th>
<th>Risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>100</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>40</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>30–50</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>30</td>
</tr>
<tr>
<td>Stroke*</td>
<td>30</td>
</tr>
<tr>
<td>High cholesterol‡</td>
<td>30</td>
</tr>
</tbody>
</table>

Based on data from *the UKPDS (42,44);†Haffner (49) and Laakso (50);‡the lipid-lowering trials (46–48).
plications. The results confirmed that the lowering of blood glucose is beneficial for preventing diabetic complications, but that the treatment effect on cardiovascular disease was limited. There was no evidence of any glycemic threshold for any of the microvascular or cardiovascular complications.

Although the UKPDS offered powerful support for the glucose toxicity hypothesis, some questions remain unanswered (43). For example, do the results apply for elderly patients, patients with a long duration of diabetes with severe hyperglycemia, or for those who already have signs of cardiovascular disease? These questions have to be clarified in forthcoming trials. The relative effect of intensive glycemic control versus intensive cardiovascular risk factor management will be investigated in a trial proposed by the National Institute of Health that will include 10,000 type 2 diabetic subjects followed for 5 years with CHD as an end point.

CONCLUDING REMARKS
Several prospective population studies including nondiabetic and type 2 diabetic patients have convincingly shown that hyperglycemia cannot be neglected as a cardiovascular risk factor. The effect of glucose on the risk of cardiovascular events starts in the nondiabetic glucose range (<6.1 mmol/l), according to current criteria for diabetes, and hyperglycemia continues to exert its effects within the diabetic glucose range in an exponential fashion.

The UKPDS has convincingly shown that long-term complications in patients with type 2 diabetes can be prevented by the correction of glycemic control. These results are consistent with the findings of the Diabetes Control and Complications Trial on type 1 diabetic patients (38). Recent clinical trials also have shown that intensive treatment of elevated blood pressure (44,45) and high cholesterol (46–48) is beneficial for patients with type 2 diabetes. Table 3 summarizes the effects of intensive treatment of hyperglycemia and hypertension based on data from the UKPDS (42,44) and of dyslipidemia based on three recent trials (46–48). In the UKPDS, intensive treatment of hyperglycemia and hypertension reduced the risk for myocardial infarction, but the treatment effect was not statistically significant (42,44). In contrast, intensive treatment of hypertension significantly reduced stroke events (44). The lowering of total (LDL) cholesterol by simvastatin treatment reduced the risk of CHD by 55% in the Scandinavian Simvastatin Survival Study (P = 0.002) (46), by 25% in the Cholesterol and Recurrent Trial (P = 0.05) (47), and by 19% in the Long-Term Intervention with Pravastatin in Ischaemic Disease Study (NS) (48).

The absolute reduction in risk does not depend only on the percentage reduction of a risk factor, but also on the prevalence of this risk factor. Obviously, all type 2 diabetic patients are hyperglycemic, but <50% have hypertension. High cholesterol levels (>6.2 mmol/l) could be even more uncommon in type 2 diabetic patients (49,50). Therefore, even if the intensive treatment of hypertension and dyslipidemia seems to yield greater reduction in the relative risk, the total number of patients benefiting from therapy is lower compared with those benefiting from intensive treatment of hyperglycemia. Given the fact that in the UKPDS, none of the treatment modalities was particularly effective in reducing glucose, this underestimates the true potential of the correction of hyperglycemia in the treatment and prevention of cardiovascular disease in patients with type 2 diabetes. Resolving the optimal mode of treatment with glucose-lowering agents remains a challenge for the future.

Aggressive treatment of hyperglycemia is undoubtedly indicated to retard the development of microvascular complications, but it also prevents, although to much less of an extent, macrovascular complications. In the management of type 2 diabetic patients, however, hyperglycemia should not be the only cardiovascular risk factor to be taken care of, but conventional risk factors, high cholesterol, elevated blood pressure, and smoking should also be targets of intervention.

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patients with NIDDM. Diabetes 48:1534–1539, 1999


