The Effects of Improved Glycemic Control on Complications in Type 2 Diabetes

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Type 2 diabetes is 8 to 10 times more common than type 1 diabetes, but no single large trial has established that improved glycemic control can prevent complications in type 2 diabetes. We have reviewed the results of the existing epidemiologic and clinical trial studies and have arrived at the following conclusions: (1) Strong evidence exists that improved glycemic control is effective at lessening the risks of retinopathy, neuropathy, and nephropathy in type 2 diabetes. (2) The evidence about the effect on coronary heart disease is limited and equivocal. (3) The hypoglycemic risk from improved glycemic control is significantly less in type 2 diabetes than in type 1, and weight gain seems to be modest. In conclusion, although glycemic goals should be individualized based on several clinical factors, most patients with type 2 diabetes would probably benefit from glucose lowering to a hemoglobin A1c level between 7% and 8%.

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Type 2 diabetes is a prevalent disease, affecting more than 3% of all adults and more than 10% of those older than 65 years, making it 8 to 10 times more common than type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) definitively proved that tight glycemic control could reduce the risk of onset and progression of retinopathy, nephropathy, and neuropathy in patients with type 1 diabetes, but no large, long-term trial has included patients with type 2 disease. As a result, physicians who provide primary diabetes care, most of whom are general internists and family physicians, are unsure how aggressively to treat hyperglycemia in their patients with type 2 diabetes. Although it is well recognized that type 2 diabetes leads to the same devastating complications as type 1 diabetes.

To address this question, we critically reviewed the literature on the effects of glycemic control on complications in type 2 diabetes. To attempt to retrieve all English language studies published since 1970 that were relevant to the association between glycemic control and complications in type 2 diabetes, we performed MEDLINE searches using combinations of the following keywords: diabetes, retinopathy, nephropathy, neuropathy, cardiovascular disease, atherosclerosis, weight gain, hypoglycemia, glycemic control, hyperglycemia, glycosylated hemoglobin, and blood glucose. In addition, we reviewed the reference lists of relevant articles.

All prospective cohort studies as well as randomized controlled trials of more than 3 months’ duration that assessed diabetic complication rates were selected. If similar results from a single cohort were reported in multiple publications, we included only the results with the longest follow-up. We excluded studies from our analysis that did not differentiate between patients with type 1 and type 2 diabetes, did not use adequate measures of glycemic control (eg, levels of fasting blood glucose or hemoglobin A1c [HbA1c]), or did not provide analyses of statistical significance.

MICROVASCULAR AND NEUROPATHIC COMPLICATIONS

Background

The cumulative lifetime incidence of microvascular and neuropathic complications is similarly high in type 1 and type 2 diabetes (Table 1), and the rates are nearly identical when adjusted for sever-
Clinical Trials

Three clinical trials of improved glycemic control in type 2 diabetes have been completed, 1 more than 20 years ago and 2 during the past year.

The University Group Diabetes Program (UGDP) randomized 619 patients with type 2 diabetes to variable-dose insulin, small fixed-dose insulin, or placebo and followed them up from 1962 to 1975. The difference in the average fasting glucose (FBG) level at the end of the study between the variable-dose and the other 2 groups was 2.0 mmol/L (36 mg/dL), which correlates roughly with a 1% difference in the level of HbA1c. The difference in levels of HbA1c between the 2 groups may actually have been much smaller (or larger) than 1%, however, because the FBG level was infrequently measured. At the end of an average of 13 years of follow-up, no significant differences were observed between the groups in the rates of proteinuria or retinopathy.

More recently, a trial of improved glycemic control in type 2 diabetes was performed in Kumamoto, Japan. In this study, 110 patients were randomized to intensive or conventional insulin therapy and were followed up for 6 years. The HbA1c levels at the end of the study were 7.1% vs 9.4% in the 2 groups, respectively. The intensively treated group had less retinopathy (13% vs 38% for a 69% reduction; 95% confidence interval, 14% to 20%), nephropathy (10% vs 30% for a 70% reduction; 95% confidence interval, 14% to 20%), and neuropathy (12.8% vs 64.6% increase in lower extremity vibration threshold, P = .005) than the conventionally treated group. These effects of glucose lowering were strikingly similar to those found in the DCCT.2

The Kumamoto study has several limitations. First, some of the study patients may have had absolute insulin deficiency, quite different from the hyperinsulinemia found in most patients with type 2 diabetes in the United States. Although the investigators identified a 24-hour urinary C-peptide excretion greater than 20 mg as an entry criterion, 1 of the treatment groups had a mean urinary C-peptide excretion that was below that level.
increased from 144 to 258 mg (P=NS), and in the standard-therapy group it increased from 135 to 470 mg (P=.004). Unfortunately, the authors failed to make direct statistical comparisons between the final values in the 2 groups.

There were no significant differences in retinopathy between the 2 groups at the end of 2 years in the VA trial,\textsuperscript{53} a finding that should be interpreted in light of the fact that in the Kumamoto study and the DCCT, 3 years of improved control were necessary to observe significant differences in the rates of retinopathy. A nonsignificant trend was observed in favor of intensive control in the second year of the VA trial, however, with 9.8% of intensively treated vs 18.0% of conventionally treated patients experiencing worsening retinopathy (P=.19; repeated measures analysis of variance).\textsuperscript{53}

Two factors help to explain why the Kumamoto\textsuperscript{48} and the VA\textsuperscript{51} trials found positive effects from glucose lowering, while the older UGDP trial did not: (1) the difference in glycemic control between treatment groups in the VA and Kumamoto trials was at least twice that achieved by the UGDP, and (2) the degree of hyperglycemia in the study population for the UGDP was so mild that the rates of complications at the end of the study were low in all the treatment groups, severely limiting the power of the study to detect a beneficial effect from improved control. (The mean FBG level in the UGDP was less than 8.9 mmol/L [160 mg/dL] for the first 7 years of the trial in those not treated with variable-dose insulin and was 9.4 mmol/L [169 mg/dL] by the end of the trial). In contrast, patients in the control groups for the Kumamoto and VA trials had higher glucose concentrations, levels that are more reflective of those found in most populations of patients with type 2 diabetes.\textsuperscript{5,45,51}

**Summary**

A large body of prospective observational data interpreted in light of the DCCT, as well as the results of recent clinical trials, strongly and consistently support the conclusions that hyperglycemia is the principal cause of retinopathy, nephropathy, and neuropathy in type 2 diabetes and that improved treatment of hyperglycemia is likely to delay the onset and progression of microvascular and neuropathic complications in patients with this disease.

**MACROVASCULAR COMPLICATIONS**

**Background**

The prevalence of coronary heart disease (CHD) is extremely high in patients with type 1 and patients with type 2 diabetes (Table 1). Some prospective epidemiologic studies, all of which excluded or included few patients with diabetes, have identified a high insulin level as an independent risk factor for CHD.\textsuperscript{76-80} but many others have not.\textsuperscript{81-87} This has raised theoretical concerns about improving glycemic control in patients with type 2 diabetes because improved control often results in higher serum insulin levels.\textsuperscript{88-90} A growing number of authors believe, however, that high serum insulin levels are simply a marker for an insulin-resistant state and have no direct role in the pathogenesis of atherosclerosis,\textsuperscript{71-73} but the issue of whether insulin has direct atherogenic effects has not been resolved.

**Indirect Data**

Although some experimental in vitro and animal models of atheroma formation have found that high insulin levels lead to accelerated plaque formation,\textsuperscript{74-77} clinical investigations have not supported this finding.\textsuperscript{78,80} In addition, a substantial amount of indirect data suggest that hyperglycemia may have a causal role in atheroma formation,\textsuperscript{81-85} and may have a prothrombotic effect on the coagulation cascade.\textsuperscript{86,87} In addition, improved glycemic control has been shown to lower low-density lipoprotein cholesterol levels,\textsuperscript{53,70,90,91} which theoretically should lower the risk of developing CHD for patients with diabetes.\textsuperscript{64,92}

**Epidemiologic Data**

We found 10 prospective epidemiologic studies that had analyzed the relationship between the FBG level or the HbA\textsubscript{1c} level and the risk of CHD.\textsuperscript{61,64,93-100} With few exceptions,\textsuperscript{99,100} investigators in these studies found a linear association between worsening glycemic control and an increased risk for CHD. In the most compelling study, the Wisconsin Epidemiologic Study of Diabetic Retinopathy, investigators analyzed cause-specific mortality over 10 years and found that death due to CHD was much more common in patients with worse glycemic control (relative risk, 1.10 for each 1% increase in HbA\textsubscript{1c}; 95% confidence interval, 1.07-1.17).\textsuperscript{93}

**Clinical Trials**

In 3 randomized controlled trials of glycemic control in type 2 diabetes, a sufficient number of cardiovascular events were recorded to make meaningful comparisons between treatment groups (Table 2). Too few events were recorded in the Kumamoto\textsuperscript{48} study because of the exclusion of patients with hypertension, hypercholesterolemia, and obesity. In the UGDP, no significant difference was found in the rate of myocardial infarction between the intensive and conventional treatment groups (20.6% vs 20.2%, respectively, P=1.00; Fisher exact test).\textsuperscript{45} This was despite a much higher prevalence of cardiac risk factors in the intensive treatment group.\textsuperscript{103}

In the Diabetes and Insulin in Acute Myocardial Infarction trial,\textsuperscript{102} 620 patients with type 2 diabetes who sought care because of an acute myocardial infarction were randomized to conventional or intensive glucose-lowering treatment. The intensive treatment group received a continuous insulin infusion for 24 hours followed by 3 months of multiple daily subcutaneous insulin, while the conventional treatment group continued their pre–myocardial infarction regimens. The level of HbA\textsubscript{1c} and cardiovascular mortality were lower in the intensively treated group compared with the control group after 1 year (mean HbA\textsubscript{1c}, 7.3% vs 7.7%; mortality, 18.6% vs 26.1%; P=.03; log-rank test).\textsuperscript{101}

The main limitation of the Diabetes and Insulin in Acute Myocardial Infarction trial\textsuperscript{101} was that although it randomized patients to improved vs usual glycemic control, all patients were enrolled in the highly specific setting of an acute myocar-
dial infarction, and those who were randomized to improved control were treated initially with intravenous insulin. Both factors limit the generalizability of the results of the study, especially because the functional changes of the acute peri-infarction period may be assumed to be different from those of the chronic phase of the development of atherosclerosis. Nevertheless, the results argue against a deleterious effect of improved glycemic control in the secondary prevention of CHD, and in fact suggest potential benefit.

In the feasibility trial of the VA Cooperative Study,103 there was a trend toward more major CHD events in the intensively treated group than in the control group (21.3% vs 11.5% suffered an event), although this finding was not statistically significant (P = .10).104 The higher number of CHD events in the intensively treated group did not seem to be related to longer follow-up in those patients, because the time to first CHD event using Kaplan-Meier estimates was slightly shorter in them, although, once again, the difference between the 2 arms was not statistically significant (P = .13). The study was obviously limited by its small sample and relatively short duration.

In the DCCT,102 cardiovascular events were monitored in patients with type 1 diabetes, although few events were recorded because of the young age and lack of hypertension or hypercholesterolemia in the study patients.102 The rate of major cardiac events was much lower in the intensively treated group, although the difference fell just short of statistical significance (0.06 vs 0.29 events per 100 patient years, \(P = .06\); Fisher exact test).102

**Summary**

Substantial evidence is lacking for a beneficial or an adverse effect on the risk of CHD of using insulin to improve glycemic control in type 2 diabetes. Theoretical considerations seem to favor a beneficial effect, and observational studies have shown a strong consistent association between improved glycemic control and a decreased risk of CHD, but limited clinical studies have had conflicting results.

**OTHER POTENTIAL DRAWBACKS TO IMPROVED CONTROL**

**Hypoglycemia**

Among 3 clinical trials, hypoglycemia has consistently been found to be less common in type 2 than in type 1 diabetes. In the VA trial, episodes of severe hypoglycemia were extremely rare (5 events in the intensive group vs 2 in the standard group, 0.03 vs 0.01 episodes per patient per year, \(P > .05\)).105 In the Kumamoto study,48 during 7 years of follow-up, there were no major episodes of hypoglycemia requiring hospitalization or the assistance of another person.48 These rates are consistent with a retrospective cohort study from Tennessee that estimated the rate of hypoglycemia among elderly patients with type 2 diabetes taking sulfonylureas to be 0.02 episodes per patient per year.105 In comparison, the DCCT recorded 0.62 episodes of severe hypoglycemia per patient per year in the intensively treated group and 0.19 in the standard therapy group.2

Preliminary reports from the United Kingdom Prospective Diabetes Study (UKPDS)109 have revealed higher rates of hypoglycemia than those found in the VA51 or the Kumamoto48 trials. Major hypoglycemic episodes occurred in 0.8%, 0.5%, and 1.4% of patients per year among those allocated to sulfonylureas, metformin, and insulin, respectively, compared with 0.2% of those continuing with diet therapy.106 This is a result of the lower glycemic goals that the UKPDS set for its intensively treated group. Whereas the intensively treated group in the UKPDS had an average HbA1c level of 6.3% after 3 years,106 the corresponding values in the intensively treated groups in the other trials were all more than 7.0% (7.3% in the VA trial,51 7.1% in the Kumamoto study,48 and 7.1% in the DCCT).102

**Weight Gain**

Weight gain from intensifying glucose-lowering regimens is a primary concern among many caregivers and patients.107 While some studies have found that modest weight gain accompanies improved control,108,109 other studies have not.45,51 Metformin has consistently been shown to cause less weight gain than insulin or sulfonylureas.70,110

**Quality of Life**

In a randomized trial to evaluate adding bedtime insulin to sulfonylurea therapy, patients with type 2 diabetes who intensified their regimens had an improved sense of well-being in addition to a lower level of HbA1c.111 In addition, achieving improved glycemic control is likely to be less disruptive of daily activities for patients with type 2 diabetes than for those with type 1 because there is less chance that

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**Table 2. Patients With CHD Outcomes in Major Clinical Trials of Improved Glycemic Control**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of Diabetes</th>
<th>No. of Patients</th>
<th>Duration, y</th>
<th>Outcome Measure</th>
<th>Tight Control</th>
<th>Usual Control</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGDP</td>
<td>2</td>
<td>619</td>
<td>12.5</td>
<td>Myocardial infarction</td>
<td>20.6%</td>
<td>20.2%</td>
<td>1.00</td>
</tr>
<tr>
<td>VA CSDM</td>
<td>2</td>
<td>153</td>
<td>2.3</td>
<td>CHD events</td>
<td>21.3%</td>
<td>11.5%</td>
<td>0.10</td>
</tr>
<tr>
<td>Kumamoto</td>
<td>2</td>
<td>110†</td>
<td>6.0</td>
<td>Myocardial infarction or angina</td>
<td>(n=1)</td>
<td>(n=1)</td>
<td>. .</td>
</tr>
<tr>
<td>DIGAMI</td>
<td>Mixed‡</td>
<td>620§</td>
<td>1.0</td>
<td>Mortality</td>
<td>18.6%</td>
<td>26.1%</td>
<td>0.03</td>
</tr>
<tr>
<td>DCCT</td>
<td>1</td>
<td>1441†</td>
<td>6.5</td>
<td>CHD events</td>
<td>0.06§</td>
<td>0.29§</td>
<td>0.06</td>
</tr>
</tbody>
</table>

\*CHD indicates coronary heart disease; UGDP, University Group Diabetes Program; VA CSDM, Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes; Kumamoto, study conducted in Kumamoto, Japan; DIGAMI, Diabetes and Insulin in Acute Myocardial Infarction; and DCCT, Diabetes Control and Complications Trial. Ellipsis indicates not applicable.

†Patients without hypertension or hypercholesterolemia.
‡Type 2, 85%; type 1, 15%.
§Patients enrolled when they sought treatment because of an acute myocardial infarction.
||Rate per 100 patient years.
a patient with type 2 diabetes will require more than 2 injections per day to achieve a near-normal level of HbA1c.31 Even among patients with type 1 diabetes in the DCCT, there was no difference in quality-of-life scores between the intensive and the conventional treatment groups.112

Summary

The evidence suggests that neither hypoglycemia, weight gain, nor changes in quality of life are likely to meaningfully affect the overall risk-benefit ratio of improved control in type 2 diabetes.

CONCLUSIONS

The preceding review allows us to make the following conclusions:
1. A large body of epidemiologic and basic science data, together with recent clinical trial data, provide strong, consistent evidence that improved glycemic control is likely to prevent or delay retinopathy, nephropathy, and neuropathy in type 2 diabetes.
2. No convincing evidence exists that improved glycemic control with insulin treatment worsens CHD in patients with type 2 diabetes. Indirect and small-scale trial data on this question have been equivocal. Overall, there is a much stronger epidemiologic association between poorly controlled hyperglycemia and increased rates of CHD than there is between higher insulin levels and CHD.
3. Strong evidence exists that hypoglycemia, which has been the only significant risk identified in association with improved control in type 1 diabetes, is 10 to 100 times less common in patients with type 2 than it is in patients with type 1 diabetes as long as the goals for the level of HbA1c are set no lower than 7.0%.
4. Although only a large, randomized trial can definitively establish the exact benefit-risk ratio of improved glycemic control, and although there is some uncertainty about a possible increased risk of CHD, we believe that the evidence for the prevention of microvascular complications and their associated disability is compelling. Therefore, when most patients with type 2 diabetes, HbA1c levels should be lowered to the levels achieved in recent clinical trials (7.0%-8.0%). Treatment goals should be adjusted for some patients based on individual clinical factors (see the “Comment” section). These conclusions agree with recent guidelines published by the American Diabetes Association.113

Several patient factors, shown in Table 3, might be expected to affect the risks and benefits of glucose lowering in type 2 diabetes. For example, patients with diabetes and a family history of diabetic nephropathy, who as a result of such family history would have a 3 to 4 times higher risk of developing nephropathy,114,115 might be expected to benefit more from improved control. Similarly, patients who at the time of the diagnosis of diabetes have early retinopathy and so a significantly higher risk of subsequent vision loss15 would also be expected to benefit more from glucose lowering.

Age at onset of type 2 diabetes would also be expected to significantly affect the risk-benefit equation. Whereas a 55-year-old woman with newly diagnosed type 2 diabetes would have a very high risk that severe microvascular complications would develop during her remaining 18 years of life expectancy, a 70-year-old man with newly diagnosed type 2 diabetes might be expected to die of CHD before microvascular complications develop that were severe enough to affect his quality of life.117,118

The issue of aggressive glycemic control in patients with type 2 diabetes is thus a complex balance between risks and benefits, which to some extent should be individualized. In this way, it resembles the controversy over postmenopausal hormone replacement. In both situations, the potential public health benefits are large and a considerable body of evidence suggests that the benefits of therapy are likely to outweigh the risks. In both situations, however, no data exist from large, randomized controlled trials to clearly define the balance between the risks and benefits.119

Only 1 clinical trial of improved glycemic control, the UKPDS,106 is in progress because the proposed full-scale VA trial has not received funding (Nicholas Emanuele, MD, personal communication, January 1997). Results from the UKPDS are expected in 1998,110 but 2 issues may limit its ability to measure the effects of improved glycemic control. First, the study has enrolled a preponderance of patients with mild levels of hyperglycemia, so it is likely to seriously underestimate the benefits that improved control might offer to the majority of patients with type 2 diabetes who have much higher levels of hyperglycemia.5,54,55 This is because the risk of microvascular complications does not rise dramatically until HbA1c levels are greater than 8%,5,24,48,120 yet the mean level of HbA1c, in the UKPDS control group after 9 years of observation is only 7.5% and has been even lower for much of the duration of the study.110 In addition, because the UKPDS was designed to compare various therapeutic agents rather than to assess the effects of improved control on complications, it may be difficult to clearly ascertain the effects of lower serum glucose levels.121

Patients with type 2 diabetes should be informed of the evidence about the benefits and risks of improved glycemic control and should participate in the decision of how aggressively their hyperglycemia should be treated. Even small reductions in the levels of HbA1c for most patients can be viewed as positive steps in their preventive health care.

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