Does Lowering of Blood Glucose Improve Cardiovascular Morbidity and Mortality?

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One of the most important questions in diabetes management is whether long-term glycemic control can reduce the risk for micro- and macrovascular complications in diabetes. Dr. Hadler in this issue of the Clinical Journal of the American Society of Nephrology raises his concerns about the use of glycosylated hemoglobin (HbA1c) as a surrogate marker of diabetes control and questions whether lowering HbA1c with the currently available oral hypoglycemic agents makes a clinically important long-term outcome difference for patients with type 2 diabetes. He is particularly concerned about the lack of evidence of cardiovascular risk reduction with HbA1c reduction in patients with type 2 diabetes. He further comments that “we were blinded” by the results of Diabetes Control and Complications Trial (DCCT) that showed reduction in microvascular complications after meticulous blood glucose control. However, it took 17 yr before any discernible advantage in terms of macrovascular disease was documented and the results are “far from a dramatic advance” in patients with type 1 diabetes; hence, one should not expect any more benefit in the middle-aged population with insulin resistance. He further cited the United Kingdom Prospective Diabetes Study (UKPDS), in which, after several years of intervention, there was no significant improvement in macrovascular complications. He questions the validity of UKPDS secondary analysis and challenges the new screening guidelines for detection and treatment of diabetes. Dr. Hadler supports his argument of lack of beneficial effects of effectiveness of oral hypoglycemic agents by reviewing A Diabetes Outcomes Progression Trial (ADOPT) results that showed relatively modest overall beneficial effects and an unexpected finding of higher fracture rates in women. Finally, he admonishes that in our focus of bringing down HbA1c we are exposing our patients to higher risk for adverse effects such as weight gain, hypoglycemia, and fractures: “...talk about missing the forest for the trees.”

We address some of the issues raised by Dr. Hadler and express our belief that improved glycemic control in patients with type 2 diabetes should be the therapeutic goal given the available evidence at this time. Let us take the question of HbA1c as a surrogate marker first. We agree that surrogate markers are not perfect and that a surrogate predicted outcome will be reliable only if there is a validated causal connection between a change in the surrogate and the clinically important outcome and if the surrogate fully captures all of the effects of treatment on that outcome. That is precisely the reason that we need to assess far more than a single study to make a decision about the adequacy of any surrogate marker. We also agree that a randomized trial designed to determine the effect of an intervention on a well-defined clinical outcome of unequivocal importance to patients is the only definitive solution to the surrogate outcome dilemma. However, when patients’ risks for serious morbidity or mortality are high, this “wait and see” strategy may result in serious health issues. Surrogate markers are cost-effective, can be reliable, and, if used appropriately, can provide very useful information. Because even Dr. Hadler admits that definitive outcomes take a long time to develop, we have essentially two choices: Either we (1) wait for the “perfect” study to be done for the longest period of time and once incontrovertible outcome data become available only then change our practices or (2) use our clinical judgment and available evidence to support our clinical decisions. Despite its limitations, we believe that HbA1c is the best available method of measuring glycemic status, and several studies have demonstrated its dose–effect relationship with both micro- and macrovascular complications. Numerous studies have demonstrated unequivocally that higher HbA1c is associated with an increased risk for complications (1–6). This has been reaffirmed by large, multicenter, prospective studies that have shown that lowering of HbA1c is associated with lessening of complications (7–10). On the basis of these data, we believe that HbA1c does fulfill the criteria of an excellent surrogate marker and should be used, within reason, as a measure of glycemic control to reduce longer term diabetes-related complications. Additional studies in different patient populations may help to define the age-, race-, and gender-specific normal values and thus may change the absolute goals, but trends and consequences associated with hyperglycemia can be reliably measured by changes in HbA1c (11).

Dr. Hadler did admit that there was significant reduction in morbidity and mortality that in our focus of bringing down HbA1c, we are exposing our patients to higher risk for adverse effects such as weight gain, hypoglycemia, and fractures: “...talk about missing the forest for the trees.”
in microvascular complications with reduction in HbA1c, but he focused primarily on the relatively modest macrovascular effects. Let us examine the microvascular effects first. Type 1 diabetes is associated with long-term complications that affect the eyes, kidneys, and peripheral and autonomic nervous systems (1–8). Hyperglycemia seems to play a central role in the pathophysiology of these complications (12). Epidemiologic studies have demonstrated a strong association between the level of hyperglycemia and the occurrence of these diabetic complications. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) enrolled a total of 10,135 patients who had diabetes, were receiving primary care in an 11-county area of southwestern Wisconsin, and were identified by chart review during 1979 to 1980. The study demonstrated a higher prevalence of retinopathy and nephropathy in patients with type 1 diabetes (2–4). Prevalence of retinopathy increased with duration of diabetes, from 6% at 4 yr to 73% at 14 yr. Risk for developing retinopathy increased with increasing duration, worse glycemic control, and age of onset up to 20 yr. The authors commented that improvements in diabetes care leading to better glycemic control may have contributed to the much lower prevalence and reduced severity of retinopathy observed than what would have been expected on the basis of a previous report from the same region of Wisconsin (13).

The data obtained from DCCT were the first long-term prospective evidence of reduction in complications associated with diabetes. The study demonstrated a 56 to 70% reduction in retinopathy, neuropathy, and nephropathy with approximately a 2% reduction in HbA1c during a mean intervention period of 6.5 yr (conventional versus intensive) (7).

This outcome was associated with increased hypoglycemic episodes but clearly demonstrated that hyperglycemia was associated with significant microvascular complications and that reduction of hyperglycemia was preventive. These effects are not trivial, and they were associated with a significantly reduced morbidity and an improved quality of life. The same findings have been reproduced by other prospective trials, and, in general, a 1% reduction in HbA1c is associated with an approximately 20 to 37% reduction in risk for microvascular complications (7–10).

The evidence described indicates a microvascular risk benefit with HbA1c reduction in both type 1 and type 2 diabetes; however, emerging evidence suggests a macrovascular risk reduction as well. Epidemiologically, Balkau et al. (14) combined the results of three large European studies and came to the conclusions that men in the upper 20% of the 2-h glucose distributions and those in the upper 2.5% for fasting glucose had a significantly higher risk for all-cause mortality in comparison with men in the lower 80% of these distributions, with age-adjusted hazard ratios of 1.6 (95% confidence interval [CI] 1.4 to 1.9) and 2.0 (95% CI 1.6 to 2.6), respectively, for the upper 2.5%. For death from cardiovascular and coronary heart disease, men in the upper 2.5% of the 2-h and fasting glucose distributions were at higher risk, with age-adjusted hazard ratios for coronary heart disease of 1.8 (95% CI 1.4 to 2.4) and 2.7 (95% CI 1.7 to 4.4), respectively. They concluded that if early intervention aimed at lowering blood glucose concentrations could be shown to reduce mortality, then it would be justified to lower aggressively the levels of both 2-h and fasting glucose, which define diabetes. Recently, Shankar et al. (15) reported that elevated HbA1c is associated with higher risk for all-cause and cardiovascular mortality in patients with type 1 diabetes. The DCCT/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study demonstrated that intensive insulin treatment reduces the risk for cardiovascular disease (CVD) among patients with type 1 diabetes. One of the most important goals of the EDIC trial was the prospective evaluation of the long-term effects of differences in previous diabetes treatment (conventional versus intensive) during the DCCT on the subsequent development and progression of CVD in patients with type 1 diabetes. The EDIC trial demonstrated that, as compared with conventional therapy, intensive insulin therapy reduced the risk for any CVD by 42% and for nonfatal myocardial infarction, stroke, or death from cardiovascular causes by 57%. Furthermore, improved glycemic control, as assessed by the decrease in HbA1c values during the DCCT, seemed to account for much of the cardiovascular benefit attributed to intensive insulin therapy. The results strongly suggest that the mean of 6.5 yr of intensive diabetes therapy during the DCCT had a sustained effect on ameliorating the risk for CVD (8). Although Dr. Hadler pointed out that it took 17 yr to show this difference, this conclusion is neither entirely true nor unexpected. The “cumulative incidence for any predefined cardiovascular outcome” curves for intensive versus conventional therapy started separating within 2 yr of follow-up, favoring intensive control. Development of macrovascular disease takes time, and one would expect a prolonged time course before developing a clinically measurable outcome. Also, one must bear in mind that this was not a straightforward comparison of a conventional with an intensive therapy group. Once patients started follow-up, both groups received the intensive insulin regimen. This study design could have been the cause of the occurrence of fewer overall events and the reason for the delay in expression of macrovascular complications, thus supporting the notion that intensive therapy is beneficial. Similarly, DCCT/EDIC (16) showed that after 6 yr, the carotid intima-media thickness was significantly greater in patients with diabetes than in control subjects. The mean progression of the intima-media thickness was significantly less in the group that had received intensive therapy during the DCCT than in the group that had received conventional therapy.

Dr. Hadler’s expressed his disappointment with the UKPDS findings that despite its a priori aim to induce cardiovascular risk reduction, it failed to show a statistically significant difference at the end of the follow-up period. We draw attention to the fact that the UKPDS clearly showed a significant reduction in microvascular disease but also showed a trend toward reduction in cardiovascular events as well. The P value did not reach the <0.05 cutoff, but the direction was clear with a 16% reduction in CVD (P = 0.052). This was achieved despite a relatively modest difference of...
HbA1c between the two arms of the study (median HbA1c 7% in intensive versus 7.9% in the conventional arm).

The UKPDS published their follow-up observational analysis that showed highly significant associations between the development of each of the complications of diabetes, including mortality, across the wide range of exposure to glycemia that occurred in patients with type 2 diabetes (17). This association remained after adjustment for other known risk factors, including age at diagnosis, gender, ethnic group, systolic BP, lipid concentrations, smoking, and albuminuria. Each 1% reduction in HbA1c was associated with a 37% decrease in risk for microvascular complications and a 21% decrease in the risk for any end point or death related to diabetes. These results suggest that the effect of hyperglycemia itself may account for at least part of the excess cardiovascular risk observed in patients with diabetes compared with individuals without diabetes beyond that explained by the conventional risk factors of dyslipidemia, hypertension, and smoking. The rate of increase of relative risk for microvascular disease with hyperglycemia was greater than that for myocardial infarction, which emphasizes the crucial role of hyperglycemia in the cause of small-vascular disease and may explain the greater rate of microvascular complications seen in populations with less satisfactory control of glycemia. Although Dr. Handler was not very impressed with the degree of association between glycemic control and macrovascular events, we believe that the study does emphasize the strong relationship between glycemic control and all diabetic complications and thus underscores the need for tighter control.

The increased risk for cardiovascular events in type 2 diabetes cannot be explained simply on the basis of traditional cardiovascular risk factors (17) and may in part be related to the clustering of metabolic and inflammatory factors (metabolic syndrome) in patients with diabetes (18,19). This syndrome is believed to have a genetic basis, but the precise genetic/molecular pathways involved are unknown (20). A number of key molecular signals that may modulate accelerated atherosclerosis in type 2 diabetes have been identified. Functional single-nucleotide polymorphisms have been discovered in genes that regulate these pathways, and many are associated with an increased risk for atherosclerosis. Whether hyperglycemia plays a role in the pathophysiology of atherosclerosis mediated through activation of inflammatory molecules is an area of active investigation. However, this association, if it turns out to be true, would explain the cause–effect relationship and support the importance of early and aggressive glucose lowering in all patients with type 2 diabetes.

Finally, the issue of safety of the currently available hypoglycemic drugs is raised, and we agree that this is a very important question. Does lowering of blood glucose with the currently available oral hypoglycemic agents result in more harm than benefits? Dr. Hadler’s arguments remind us of the editorial by Siperstein et al. (21) published in the New England Journal of Medicine in 1977 that raised the question of whether the benefits of tight control are sufficiently proved to warrant the attendant risks for hypoglycemia. Now, 30 yr later, we believe that maintenance of euglycemia is associated with reduction of microvascular complications in patients with both type 1 and type 2 diabetes and that the risk for hypoglycemia can be treated with better and more sophisticated monitoring and treatment modalities. Siperstein and his colleagues had never questioned the importance of glucose control but wanted clinicians to balance the risks associated with achieving euglycemia with the known adverse effects of the therapeutic interventions available in the mid-1970s. The same argument may apply today. There are substantial data supporting the association between hyperglycemia and CVD, and there are emerging data that cardiovascular outcomes may improve with reduction in HbA1c. Achieving this outcome with minimum adverse effects is the challenge that we face with currently available oral hypoglycemic agents. Nevertheless, the availability of strong evidence supporting the microvascular risk reduction in itself is a sufficient reason to aim for better glycemic control. As more data about the cardiovascular outcomes become available, we should reassess our position. In this regard, the discussion in the scientific community between the Food and Drug Administration (FDA) and GlaxoSmithKline regarding rosiglitazone and its risk for cardiovascular morbidity is instructive (22,23). The Food and Drug Administration panel pointed out that currently all oral hypoglycemic agents are approved for glycemic control. Furthermore, there is “progressive worsening of glycemic control over time in diabetic patients and thus long-term trials will probably need to compare one drug within a multi-drug regimen with other available therapies, making demonstration of the effect of any single drug a formidable task.” The GlaxoSmithKline response raised the issue that the higher risk for myocardial ischemic events with rosiglitazone was observed in only placebo-controlled trials; in studies comparing different therapeutic interventions, there was no excess risk with rosiglitazone as compared with metformin and sulfonylureas, and there was no statistically significant difference among the three treatment groups. Does this mean that all three of these hypoglycemic agents may cause an increase in ischemic heart disease? These analyses were done on trials reported in Nissen’s meta-analysis (24), and those trials differed widely in their aims, study populations, duration of exposures, etc. Thus, at this time, there are no high-quality data that would substantiate this claim. The UKPDS has demonstrated that there is a natural progression of disease in patients with type 2 diabetes, thus requiring the use of more agents to control hyperglycemia over time. Because we believe that hyperglycemia is associated with higher risks for complications, we argue that the best current approach is to use the most effective and safest available agents with the goal of achieving euglycemia for the longest period of time with the least number of adverse effects. The search for safe and effective oral hypoglycemics should continue, but on the basis of the current evidence, the benefits of using hypoglycemic agents far outweigh the potential risks of drug-associated complications. We agree with Ness, who noted that “uncertainty along the
way is the hallmark of science and the price of progress” (25). Concato (26) rightly pointed out that “progress in science is iterative and incremental...putting what we know into practice would prevent more disease than worshipping at the altar of randomized trials.”

In summary, we believe that hyperglycemia is a risk factor in a dose-dependent manner for both micro- and macrovascular complications in both type 1 and type 2 diabetes, and HbA1c is an excellent measure of glycemic control. The HbA1c value is the best surrogate marker that we have right now. Clearly, clinical judgment should be used when treating individual patients, such as the example cited in Dr. Hadler’s article, but the importance of glycemic control should not be minimized. In the absence of any “threshold” of blood glucose at which the complications occur, we believe that lowering of blood glucose to as close to the normal range as possible with safest drugs available should be the goal of both patients and their physicians.

Disclosures
None.

References