Diabetic Macrovascular Disease
The Glucose Paradox?
Peter Libby, MD; Jorge Plutzky, MD

The cardiology community is awakening to a rampant epidemic of type II diabetes and its common companion, the metabolic syndrome. As the ponderosity of the US population increases, the morbid constellation of obesity, hypertension, glucose intolerance, insulin resistance, and dyslipidemia (characterized by abundant triglyceride (TG)-rich lipoproteins, low levels of atheroprotective high-density lipoprotein [HDL], and small, dense low-density lipoprotein [LDL] particles) is on the rise.1 Pioneering work from several laboratories has provided us with pathophysiological insight for understanding some of diabetes’ vascular complications. In the face of hyperglycemia, glucose molecules conjugate by a nonenzymatic mechanism with the reactive side chains of the amino acid lysine on protein molecules (Figure). Through a series of well-understood chemical reactions, this nonenzymatic glycation can ultimately generate higher molecular weight condensates known as advanced glycation end products (AGE).2,3 The formation of caramel from sugar provides a simple analogy for this process. Such reactions can be quite pervasive—occurring both inside and outside the cell, chemically modifying and potentially altering the functions not just of proteins, but of lipids and nucleic acids as well.

Researchers have recognized the buildup of AGE-modified macromolecules for many years. However, recent discoveries have furnished a novel link between AGE-modified proteins and altered behavior of cells involved in arterial disease. Stern and colleagues characterized a cell surface receptor for binding AGE, RAGE (RAGE).2 A number of groups have shown that RAGE, one might logically assume that strict glycemic control significantly reduces the level of this indicator-glycated protein. However, the plausible hypothesis that tight glycemic control would protect against diabetic vascular complications. Indeed, several important clinical trials have demonstrated that stringent glycemic control and ligands for AGE signaling decreased levels of matrix-degrading proteinases and increased levels of interstitial collagen, the crucial protector of the integrity of the plaque’s fibrous cap. These important new experiments not only advance our knowledge of the pathophysiology of experimental atherosclerosis in these diabetic, atherosclerosis-prone mice, but also point to a new therapeutic target of considerable interest, given the epidemic of diabetic vascular disease we now confront.

Formation of AGE presumably relates to the level of glycemia. Indeed, our commonly used clinical index of glycemic control, hemoglobin A1C, measures a protein (hemoglobin) that has undergone nonenzymatic glycation, and correlates with AGE levels. Treatments that lower blood sugar reduce the level of this indicator-glycated protein. Given this link between glycemic control and ligands for RAGE, one might logically assume that strict glycemic control would protect against diabetic vascular complications. Indeed, several important clinical trials have demonstrated that stringent glycemic control significantly reduces the incidence of microvascular complications of diabetes such as nephropathy, retinopathy, and neuropathy.6–9

However, the plausible hypothesis that tight glycemic control would likewise reduce the risk of macrovascular complications of diabetes such as myocardial infarction has thus far eluded broad clinical proof. A number of well-conducted clinical trials, such as the University Group Diabetes Program (UGDP) and the United Kingdom Prospective Diabetes Study (UKPDS), among others, have found only limited, if any, relationship between glycemic control and diabetic macrovascular manifestations (Table 1).6–9 In stark contrast, numerous studies consistently show that pharmacological interventions that target the dyslipidemia and hypertension associated with type II diabetes can handily reduce risk of macrovascular complications in such patients. Thus, the goal of proving that glycemic control can also lower risk of heart attack or stroke still seems out of reach.8,9

Clinical trials indicate that strict glycemic control forestalls microvascular disease to a greater extent than macrovascular
manifestations. Multiple factors may contribute to this disparity (Table 2). The studies conducted so far may well have just lacked sufficient power to settle the question, as they often show a trend for decreased cardiovascular events but fall short of achieving statistical significance. Indeed, the intensive antidiabetic treatment arm in the UKPDS reported a 16% reduction in myocardial infarction (MI) \( (P=0.052) \). Even if underpowering contributes to this possible glucose paradox, it appears that current antidiabetic treatments do not match the impact of treatments like statins or interruption of angiotensin II signaling (Table 1).

The specific interventions used to lower glycemia may also contribute to the inability to show decreases in macrovascular end points. With some antidiabetic treatments, untoward effects may counterbalance potential benefits. Generally, interventions that increase insulin supply (eg, insulin itself and sulfonylureas) have proven less promising for limiting cardiovascular complications than those that improve glucose utilization or reduce insulin resistance. Indeed, in one arm of UKPDS, metformin monotherapy decreased MI by 39\% \( (P=0.01) \) in an overweight subgroup, a benefit not seen in patients requiring metformin plus sulfonylureas or insulin.\(^{10}\) Thiazolidinediones (the “glitazones”) hold considerable promise as insulin sensitizers and merit careful clinical evaluation for cardiovascular benefit.\(^{11}\)

Perhaps too short a duration or too tardy institution of better glycemic control accounts for the lack of effect on end points related to atherosclerosis in patients with diabetes. We know that the metabolic derangements in type II diabetes precede the development of frank diabetes by many years. Thus, hyperglycemia may have gradually wrought its damage over time in such a way that the duration of intervention...
afforded in clinical trials does not suffice to reverse its ravages. However, over a similar duration of treatment (3 to 5 years), other interventions can reduce macrovascular events, as shown with statins, fibrates, and agents that disrupt angiotensin II signaling.

The expectation that strict glycemic control alone can mitigate atherosclerosis in type II diabetes does not take into account the multiplicity of contributory metabolic and inflammatory factors (Figure). Adipose tissue itself can release proinflammatory stimuli that may well produce inflammatory factors (Figure). Adipose tissue itself can release proinflammatory stimuli that may well produce inflammatory factors (Figure). Adipose tissue itself can release proinflammatory stimuli that may well produce inflammatory factors (Figure).

**TABLE 2. Some Potential Contributors to the Glucose Paradox**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
<th>Targeted Risk Factor</th>
<th>Risk Reduction, Primary Cardiovascular End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>4S</td>
<td>LDL</td>
<td>−42%</td>
</tr>
<tr>
<td></td>
<td>HPS/Diabetes/No history CAD</td>
<td>LDL</td>
<td>−≈35%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>CARE</td>
<td>LDL</td>
<td>−27%</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>VA-HIT</td>
<td>TG/HDL</td>
<td>−24%</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>DAIS</td>
<td>TG/HDL</td>
<td>−23%</td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feldopine plus</td>
<td>HOT</td>
<td>Diastolic hypertension</td>
<td>−51% (diastolic 90 mm Hg vs 80 mm Hg)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>HOPE</td>
<td>BP</td>
<td>−25%</td>
</tr>
<tr>
<td>Losartan vs atenolol</td>
<td>LIFE</td>
<td>BP</td>
<td>−24%</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>BIP</td>
<td>BP</td>
<td>−42%</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive therapy</td>
<td>UGDP</td>
<td>Glucose</td>
<td>Tolbutamide: increased cardiovascular risk, stopped; no difference in all other groups</td>
</tr>
<tr>
<td>Intensive insulin</td>
<td>DCCT (type I diabetes mellitus)</td>
<td>Glucose</td>
<td>Macrovascular: −42%</td>
</tr>
<tr>
<td>Metformin</td>
<td>UKPDS (overweight)</td>
<td>Glucose</td>
<td>−39%</td>
</tr>
<tr>
<td>Sulfonpylurea/Insulin</td>
<td>UKPDS</td>
<td>Glucose</td>
<td>−16% (NS)</td>
</tr>
<tr>
<td>Met/sulfonpylurea</td>
<td>UKPDS</td>
<td>Glucose</td>
<td>+96% (diabetes mellitus–related mortality)</td>
</tr>
</tbody>
</table>

This table summarizes some studies that have examined the impact on cardiovascular events in diabetic subjects of treatment targeting various risk factors for atherosclerosis (original references cited in Beckman et al). Inherent limitations exist in comparing data from populations in different studies, with variable factors including genetic background, conventional therapies employed, baseline risk, and differing levels of other variables. Regardless, demonstration of reduced cardiovascular risk by lipid and blood pressure interventions has proved easier and more apparent than strict glycemic control. Many factors, including trial design, may contribute to this apparent paradox, as discussed in the text and Table 2. All risk reductions shown achieved statistical significance except as noted.

HPS indicates Heart Protection Study; CAD, coronary artery disease; CARE, Cholesterol And Recurrent Events; VA-HIT, Veterans Administration HDL Intervention Trial; DAIS, Diabetes Atherosclerosis Intervention Study; HOT, Hypertension Optimum Treatment; HOPE, Heart Outcomes Prevention Evaluation; LIFE, Losartan Intervention For Endpoint reduction in hypertension; BIP, Bezafibrate Infarction Prevention; UGDP, United Kingdom Perspective Diabetes study; BP, blood pressure; Met, metformin; and NS, not statistically significant.

Moreover, the complex pattern of dyslipidemia commonly encountered in type II diabetes may also promote arterial inflammation and hence atherogenesis. Although patients with type II diabetes often have average levels of LDL, they typically have qualitative abnormalities in these particles. The small, dense LDL typical of type II diabetes has particular susceptibility to oxidative modification and, therefore, triggering of inflammation. The TG-rich lipoproteins, such as β-very-low-density lipoprotein, may also incite inflammation by activating the transcription factor NF-κB, an orchestrator of the expression of proinflammatory genes related to atherogenesis. Low levels of HDL rob the vessel wall of a protective particle that promotes efflux of lipid from the arterial wall and carries antioxidant enzymes. Thus, the multifactorial complexity of diabetic vascular disease may
stymie the ability of strict glycemic control to forestall atherosclerotic events. Although the study of Bucciarelli et al suggests an important role for RAGE in progression of atheroma, we must nonetheless acknowledge that the management of diabetic macrovascular disease requires much more than attention to glycemia.

Although we look forward to ongoing and future trials with existing antidiabetic drugs and the development of new treatments for diabetic macrovascular disease, we must not forget to implement therapies known today to prevent vascular complications of diabetes. Proven strategies include addressing the prothrombotic state with aspirin, treating dyslipidemia to values targeted by national guidelines, and achieving blood pressure goals of 130/85 mm Hg as mandated by the American Diabetes Association. Nonpharmacological lifestyle modifications, although hard to achieve in practice, can impressively improve metabolic variables in type II diabetes correlated with cardiovascular events. On the basis of exciting and novel research avenues such as those represented by the work of Bucciarelli et al, we may look forward to an “age of AGE” as a future target of therapy. In addition to a glucose paradox, we confront a “treatment paradox”: insufficient adoption of therapies that can improve macrovascular end points in diabetes. Although we await tomorrow’s advances, we must implement today our current preventive guidelines with intensified fervor to reduce the growing burden of cardiovascular morbidity and mortality among patients with diabetes.

References

Key Words: Editorials □ atherosclerosis □ diabetes mellitus □ lipid □ risk factors
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