Diabetes and atherosclerosis: is there a role for hyperglycemia?

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Abstract **Atherosclerosis is accelerated in both type 1 and type 2 diabetes. The hallmark of diabetes is the presence of hyperglycemia. In this article, we review the role of glucose in the pathogenesis of atherosclerosis. Evidence obtained from epidemiological, in vitro, and animal studies will be reviewed in an attempt to understand the complex relationship between hyperglycemia and cardiovascular risk that is emerging from clinical trials.—**Chait, A., and K. E. Bornfeldt. **Diabetes and atherosclerosis: is there a role for hyperglycemia?** ***J. Lipid Res.*** **2009. S335–S339.**

Supplementary key words glycemic control • lesion initiation • lesion progression • dyslipidemia • cardiovascular risk • epidemiology • animal studies

Atherosclerosis is the cause of a majority of cardiovascular events, and atherosclerosis is accelerated by diabetes and the metabolic syndrome. Many risk factors are associated with the metabolic syndrome and help explain the increased cardiovascular disease (CVD) in that condition (1). Because the metabolic syndrome occurs in most people with type 2 diabetes, its presence likely accounts for most of the increased incidence of CVD in type 2 diabetes (2). However, the presence of diabetes increases the risk of CVD beyond that seen with the metabolic syndrome alone (2). Moreover, CVD risk is increased in type 1 diabetes (3), in which the presence of the metabolic syndrome and these other risk factors is less common. So what is unique about diabetes that distinguishes it from the metabolic syndrome and might underlie the increased risk of atherosclerotic CVD in types 1 and 2 diabetes? The most logical explanation is hyperglycemia, which defines the diabetic state and which is common to type 1 and type 2 diabetes.

In this review, we critically examine the evidence that glucose plays a role in atherogenesis and also discuss the relative importance of glucose versus lipids. We examine the epidemiological evidence that suggests that hyperglycemia and glycemic control are CVD risk factors. We then evaluate in vitro evidence, animal studies, and clinical trials to help understand the relationship between hyperglycemia and atherosclerosis risk, and discuss the advantages and shortcomings of each approach.

EPIDEMIOLOGICAL EVIDENCE SUPPORTS AN ASSOCIATION BETWEEN GLYCEMIC CONTROL AND CARDIOVASCULAR DISEASE

Strong epidemiological evidence supports an association between glycemic control and CVD risk (4). The United Kingdom Prospective Diabetes Study (UKPDS) provided additional insights into the relationship between glycemic control and CVD in patients with type 2 diabetes, indicating a linear relationship between HbA1c and CVD endpoints, particularly myocardial infarction (5). However, the slope of the relationship between HbA1c and microvascular complications is much steeper that than for myocardial infarction, raising the question of whether glucose plays a greater role in the pathogenesis of microvascular than cardiovascular complications of diabetes. Similar but less-robust relationships have been observed in patients with type 1 diabetes (6). However, epidemiological studies only indicate associations, and provide no evidence of causality. Therefore, other approaches are necessary to understand the potential role of hyperglycemia in the pathogenesis of cardiovascular disease.

STUDIES ON ISOLATED VASCULAR CELLS SUGGEST THAT ELEVATED GLUCOSE LEVELS CAUSE A PLETHORA OF PROATHEROGENIC RESPONSES, BUT THE IN VIVO RELEVANCE OF MOST OF THESE FINDINGS AWAIT VERIFICATION

Although in vitro studies have provided important insights into potential mechanisms by which glucose might damage arterial cells or play a role in atherogenesis, these

Research in the authors' laboratories is funded by National Institutes of Health grants HL30086, HL92969, and HL18645 to A.C.; and HL62887, HL92969, and 5-2008-257 from the Juvenile Diabetes Research Foundation to K.E.B.

Manuscript received 23 October 2008 and in revised form 19 November 2008.

Published, JLR Papers in Press, November 23, 2008.
DOI 10.1194/jlr.R800059-JLR200

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studies suffer from the shortcoming that they usually examine a single mechanism in isolation, and often provide different results from those obtained with in vivo studies. Numerous studies have attempted to evaluate the role of high glucose conditions on cells of the artery wall, including endothelial cells, smooth muscle cells, and macrophages. It has been proposed that glucose might act directly, or indirectly via the generation of advanced glycation endproducts (AGEs) or reactive oxygen species. High glucose concentrations have been shown to lead to diacylglycerol accumulation and protein kinase C activation in vascular cells, and to increased glucose flux through the aldose reductase pathway. These pathways have been linked to increased inflammation via increased nuclear factor κ-B activation, for example. The most well-described glucose-induced pathways have been reviewed in detail elsewhere (7, 8), and are therefore not further covered here.

Atherosclerosis is initiated by the adhesion of monocytes to arterial endothelial cells, followed by their transmigration into the subendothelial space along a chemotactic gradient. One mechanism by which high glucose conditions may enhance this process involves activation of NFκB (9, 10), which leads to the expression of several inflammatory genes, including adhesion molecules that facilitate monocyte adhesion to endothelial cells (9). Monocytes then differentiate into intimal macrophages, which take up lipids (thereby becoming foam cells) and accumulate in the artery wall in diabetes, resulting in accelerated fatty streak formation. With time, these early fatty streak lesions are believed to develop into advanced lesions, characterized by smooth muscle cell accumulation, necrotic core formation, and lipid accumulation. Some of these advanced lesions eventually become unstable and rupture, resulting in the clinical manifestations of CVD. Interestingly, glucose alone can affect monocyte/macrophage activation in vitro. Thus, monocytes grown in high glucose conditions show evidence of increased expression of the cytokines, interleukin-1β and interleukin-6 (11). These inflammatory changes are associated with induction of protein kinase C, activation of NFκB, and increased release of superoxide, which could play a role in glucose-mediated oxidative stress (12). Auto-oxidation of glucose leads to the formation of several reactive oxygen species such as the superoxide anion, and can facilitate LDL oxidation in vitro (13). Scavenger receptors on arterial macrophages can take up modified lipoproteins, including LDL that have become oxidized as a result of glucose-mediated oxidative stress (13), or modified by AGEs (14). Moreover, AGE-modified albumin can inhibit SR-B1-mediated efflux of cholesterol to HDL (15). These findings suggest that AGE proteins in the circulation also might interfere with the functions of SR-BI in reverse cholesterol transport by inhibiting the selective uptake of HDL-cholesteryl ester, as well as cholesterol efflux from peripheral cells to HDL. Thus, alterations in the delivery and removal of lipid from macrophages by lipoproteins and other proteins that have been modified by prolonged exposure to high glucose conditions might lead to lipid accumulation and foam cell formation.

Together, in vitro studies have elucidated multiple mechanisms by which glucose might be atherogenic. However, studies on cultured cells provide only hypothesis-generating results that then have to be evaluated in vivo. There are many reasons why studies using cultured vascular cells might not mimic the responses of these cells in vivo. For example, cultured cells are often phenotypically different from those in vivo; they rapidly deplete culture media of glucose (16) and are generally not exposed to the fluctuations in glucose seen in patients with diabetes. In vivo responses are a complex result of interactions between many different risk factors, and it is often difficult to know to what extent hyperglycemia might have contributed to a specific outcome.

To what extent have the cell-culture findings on effects of high glucose levels been confirmed in an in vivo model? Although much work has been devoted to this question, only a few studies indicate a direct role for hyperglycemia, without confounding effects of lipids or other risk factors. Acute stimulatory effects of glucose infusion on leukocyte rolling and adherence to the endothelium have been demonstrated in the rat. This effect is likely due to elevated glucose per se, and could be normalized by insulin treatment (17). Another approach has been to overexpress glucose transporters (GLUT) in vascular cells to selectively increase glucose metabolism. Overexpression of GLUT-1 in arterial smooth muscle cells demonstrated that increased glucose metabolism in these cells leads to reduced apoptosis following vascular injury (18). Thus, glucose appears to directly and acutely stimulate leukocyte adherence to the vascular wall and smooth muscle accumulation. Animal models of type 1 or type 2 diabetes/insulin resistance are more complex (as is the case in humans with diabetes), because it is difficult to separate the effects of hyperglycemia from those of other atherogenic factors. Some of the in vivo models of diabetes-associated atherosclerosis are reviewed below.

STUDIES USING EXPERIMENTAL ANIMALS DEMONSTRATE A CLOSE RELATIONSHIP BETWEEN GLUCOSE AND LIPIDS

Early studies in rabbits made diabetic by the administration of alloxan resulted in marked hypertriglyceridemia, which confounded the effect of the diabetes on atherosclerosis (19). Moreover, diabetic nonhuman primates have not provided much insight into the role of glucose in the pathogenesis of atherosclerosis (20). In pigs, it has been possible to distinguish the effects of diabetes from those of hypercholesterolemia, which nearly always accompanies the onset of diabetes. Diabetic pigs do not develop atherosclerosis in the absence of hyperlipidemia. However, the presence of diabetes increases atherosclerosis in hyperlipidemic pigs (21), indicating that glucose and lipids might act through synergistic mechanisms to accelerate atherosclerosis. Although plasma cholesterol was not further elevated by diabetes, plasma triglyceride levels were increased in the diabetic hyperlipidemic pigs. Thus, the effect of lipid changes due to diabetes cannot be ruled out as a contributing factor. In another study in diabetic hyperlipidemic pigs, the increased atherosclerosis observed in the diabetic ani-

mals was again confounded by an increase in the ratio of LDL to HDL in the diabetic animals (22).

Most studies using mouse models of diabetes also have been hampered by the confounding issue of dyslipidemia. Furthermore, severe hyperlipidemia often appears to mask the effects of diabetes on atherosclerosis (23). For example, the increased atherosclerosis observed in diabetic apoE-deficient mice was associated with a proportional increase in plasma cholesterol levels (24). The presence of diabetes in severely hyperlipidemic LDL-receptor-deficient mice was not associated with an increase in atherosclerosis (25). However, a marked redistribution between LDL and VLDL levels are likely to have confounded the effects of diabetes per se. In another study, streptozotocin-diabetic LDL receptor$^{+/-}$ mice without extensive hyperlipidemia showed more lesions in the aortic arch than nondiabetic controls, even though lipid levels were similar in the two groups (26).

One mouse model that has enabled studies of the effects of diabetes alone versus those of diabetes-induced hyperlipidemia is a transgenic LDL-receptor-deficient mouse in which type 1 diabetes can be induced by a virus (27, 28). In this model, viral infection results in T-cell mediated destruction of pancreatic β?-cells expressing a viral protein transgene, closely mimicking the autoimmune destruction of these cells that occurs in type 1 diabetes in humans. In this model mouse, diabetes accelerates lesion initiation, measured as an increased macrophage accumulation and fatty streak formation, and also accelerated intraplaque hemorrhage in advanced lesions in the brachiocephalic artery (27, 28). The effects of diabetes on lesion initiation were not dependent on differences in plasma lipid levels and were most likely due to hyperglycemia or the consequences of hyperglycemia. Moreover, intense insulin therapy normalized the diabetes-accelerated lesion initiation, thus confirming that the accelerated lesion initiation was likely an effect of suboptimal metabolic control. However, in advanced lesions, hyperglycemia alone, without hyperlipidemia, was not sufficient to cause intraplaque hemorrhage and lesion disruption (28).

Mice are relatively deficient in the enzyme aldose reductase, which generates toxic products of glucose. Diabetic LDL-receptor-deficient mice with a human aldose reductase transgene developed more atherosclerosis than in the absence of the transgene (26), thus providing a potential explanation why glucose might not have the same deleterious effect in mice as in humans.

Thus, mouse models have been of value in helping suggest that hyperglycemia may play a role in lesion initiation, although lipids are required for this effect. Furthermore, hyperglycemia alone is not sufficient for lesion progression. In humans the onset of hyperglycemia often occurs many years after the onset of the lipid abnormalities related to the antecedent presence of the metabolic syndrome (29). Findings from these mouse models also suggest that the onset of overt diabetes when atherosclerotic lesions are already established can lead to intraplaque hemorrhage and lesion disruption, which might explain the high incidence of clinical cardiovascular events that occur in patients with type 2 diabetes.

CLINICAL TRIALS HAVE DEMONSTRATED THAT LIPIDS ARE MORE IMPORTANT THAN GLUCOSE, AT LEAST IN PATIENTS WITH ESTABLISHED TYPE 2 DIABETES

Randomized controlled clinical trials often are regarded as the gold standard by which to judge the effect of a particular factor in the pathogenesis of disease. However, randomized control trials have yet to provide definitive understanding regarding the role of hyperglycemia in the manifestation of CVD. Part of the problem relates to the difficulty in achieving tight glycemic control in clinical practice, and to the fact that most studies to date have not adequately distinguished the various ways of achieving glycemic control from each other.

The Diabetes Control and Complications Trial (DCCT), in which the effect of tight glycemic control was studied in young subjects with type 1 diabetes, failed to show a reduction of CVD outcomes despite demonstrating an impressive reduction in microvascular complications (30). However, few CVD events occurred during the study, in part due to the relatively young age of the subjects. The UKPDS evaluated the effect of intensive glycemic therapy in newly diagnosed subjects with type 2 diabetes. The study also failed to show a significant benefit of intensive glycemic therapy on CVD outcomes, although the 16% reduction in myocardial infarctions observed nearly achieved statistical significance (31). The subjects had low levels of HbA1C at entry, and the separation between intensively and conventionally treated groups was not very large at the end of the study. Moreover, glycemic goals were not as stringent as in current guidelines.

Two more recently completed studies had even more negative outcomes. Both the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) studies were performed in longstanding type 2 diabetic subjects with multiple cardiovascular risk factors and a high incidence of previous CVD. Aggressive glucose-lowering therapy was used in both studies to achieve targets that were lower than in the American Diabetes Association guidelines. Surprisingly, neither study showed any beneficial effect of tight glycemic control (32, 33). Moreover, increased mortality was observed in the tight glycemic control limb in ACCORD (32), possibly related to the rapidity with which glycemic control was reached, the considerable weight gain, and the use of multiple insulin injections in these subjects with longstanding diabetes and multiple CVD risk factors and a high incidence of established CVD. However, there was no suggestion of any benefit of glycemic control that would have been predicted from the epidemiological evidence. In contrast, beneficial effects of lipid lowering in subjects with established type 2 diabetes are clear (34). Thus, lipids are likely to play a more important role than glucose in patients with established type 2 diabetes.

Recent findings from the 10-year follow-up of UKPDS may shed some additional light on our understanding of the role of glycemic control on CVD. The intensively treated

group had a significant reduction in CVD events with prolonged follow-up, despite intensively and conventionally treated groups reverting to identical levels of glycemic control shortly after the end of the parent study (35). Thus, better glycemic control at the time of diagnosis of diabetes improved outcomes many years later, long after differences in glycemic control were lost. These findings are similar to those observed in the long-term follow-up of the DCCT cohort. Here, too, the effect of tight glycemic control early in the study led to beneficial outcomes many years later (36). These observations occurred despite glycemic control in the intensively treated and control groups rapidly became equivalent after the termination of the main trial, similar to what was observed in the UKPDS follow-up.

Can we extrapolate information gleaned from animal studies to help explain these seemingly paradoxical findings from randomized clinical trials? While the findings from these long-term follow-up studies have been attributed by some to "metabolic memory," it is unclear what the molecular basis of such a phenomenon might be. In mice, hyperglycemia appeared to be associated mainly with lesion initiation and had no effect on lesion progression (27). The observations in the long-term follow-up of UKDS and DCCT are consistent with these findings in mice. In both those studies, tight glycemic control was started early in the course of the disease, likely before the development of advanced lesions. Thus, lesions might have been more advanced in the control groups at the termination of both these studies, leading to earlier and more clinical events many years later.

CONCLUSIONS

Epidemiological studies have provided convincing evidence that the risk of CVD is increased by the presence of diabetes and that the increased risk is related to the extent of glycemic control. However, epidemiological studies provide no insight into causality, and are hypothesis generating. In vitro studies have provided important clues to the mechanism by which hyperglycemia might lead to atherosclerosis, but these mechanisms have not always been borne out in vivo. Moreover, in vitro studies tend to be overextrapolated and can be misleading. Although animal studies can help understand mechanisms, there are few animal models of increased atherosclerosis in diabetes that are not confounded by lipid changes. These models have clearly demonstrated that hyperglycemia alone, in the absence of some hyperlipidemia, is insufficient to accelerate atherosclerosis. Much more work is needed before we would know to what extent these studies are applicable to humans.

Randomized clinical trials can provide important information regarding the role of specific risk factors, such as hyperglycemia and glycemic control, in CVD in diabetes. However, they too have not provided conclusive evidence regarding the relation of glucose to CVD, whereas a clear beneficial effect of lipid lowering has been demonstrated by many clinical trials. Nonetheless, evidence gained from all these lines of evidence has provided a better, although incomplete, understanding of the role of diabetes in the pathogenesis of CVD and its complications. Improved mouse models and more clinical trials, for example investigating the combined effect of improved glycemic control and lipid lowering in both type 1 and type 2 diabetes, are urgently needed in order to find ways to treat or prevent cardiovascular complications of diabetes.

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