Lipids Versus Glucose in Inflammation and the Pathogenesis of Macrovascular Disease in Diabetes

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Type 1 and type 2 diabetes both accelerate cardiovascular disease, yet the triggers are likely different for the two types of diabetes. Results from large-scale clinical trials suggest that intense blood glucose control can reduce cardiovascular events many years later in patients with type 1 diabetes. In type 2 diabetes, mechanisms related to insulin resistance and obesity may be more prominent in promoting atherosclerosis. In this article, we discuss the potential effects of hyperglycemia and diabetes-induced lipid abnormalities on atherosclerosis, particularly focusing on advanced stages of atherosclerosis and evidence from mouse models. In addition, we discuss new research findings in monocyte/macrophage biology that may present intriguing new areas of research related to diabetes and atherosclerosis.

Introduction

Both type 1 and type 2 diabetes are associated with an increased risk of stroke, coronary heart disease, and peripheral arterial disease [1]. The underlying cause for many of these macrovascular complications is atherosclerosis. Rupture of advanced atherosclerotic lesions is the main culprit of cardiovascular events. The mechanisms related to accelerated atherosclerosis formation in diabetes are not well understood, yet many theories implicate both hyperglycemia and lipid abnormalities. Other factors, such as hypertension, smoking, and nephropathy, are also likely to play important roles, when present, as they do in patients without diabetes. Type 2 diabetes is generally associated with obesity and hyperlipidemia, whereas type 1 diabetes exhibits no detectable or modest lipid abnormalities [2]. Several large-scale clinical trials support an association between improved glucose control in type 1 diabetes and reduced cardiovascular-related events [3,4]. The role of glycemic control in atherosclerosis associated with type 2 diabetes is not prominent, and new theories propose that lipid deposition precedes insulin resistance in most obesity-related diabetes, and that glucose's effects may be masked by those of lipid abnormalities [2,5]. Accordingly, no direct evidence exists to suggest intense glucose control significantly reduces cardiovascular-related events associated with type 2 diabetes [6,7]. Therefore, a general effect of hyperglycemia in directly promoting cardiovascular events in diabetes is by no means well established, despite several clinical studies and many interesting in vitro observations. Furthermore, it is becoming increasingly clear that the mechanisms governing lesion initiation and those causing progression to advanced lesions are quite different.

This article addresses the concepts that hyperglycemia may play a role in promoting the early stages of atherosclerosis in type 1 diabetes, and that it is difficult to distinguish the effect of glucose from that of lipids in advanced atherosclerosis acceleration. In addition, this article addresses some of the exciting new advancements in monocyte/macrophage biology and suggests potential areas of focus for deciphering the effects of diabetes on inflammation and atherosclerosis.

Animal Models of Diabetes-Accelerated Plaque Disruption and Cardiovascular Events Are Urgently Needed

Animal models have proven valuable as a means to investigate specific mechanisms involved in the atherosclerotic disease processes. However, most studies of atherosclerosis in animals with or without diabetes are derived from models of early lesion formation [8••,9]. This is in contrast to clinically relevant advanced human lesions, in which acute cardiovascular events precipitate from rupture of destabilized

advanced plaques [10]. As yet, no one animal model exists that adequately models the processes of plaque rupture, thrombus formation, and occlusion of the lumen [9]. Therefore, there has been an effort to characterize the progression of advancing lesions in animal models, which has led to the identification of surrogate markers for unstable plaques; most notable is intraplaque hemorrhage in the absence of plaque microvessels. Several groups have identified models that present with intraplaque hemorrhage and other characteristics similar to advanced human disease. Gerrity et al. [11] identified an appropriate phenotype in the coronary arteries of hyperlipidemic streptozotocin-diabetic swine. Our laboratory pioneered investigations into the effects of type 1 diabetes on advanced lesions using a low-density lipoprotein receptor deficient ($LDLR^{-/-}$) mouse model [12].

In this $LDLR^{-/-}$ type 1 diabetic mouse model, expression of the lymphocytic choriomeningitis virus (LCMV) glycoprotein (GP) transgene is controlled by the insulin promoter. In this model (further referred to as the $LDLR^{-/-}$;GP mouse model), type 1 diabetes can be induced by infection with LCMV, resulting in T-cell–mediated destruction of GP-expressing β cells, closely mimicking the autoimmune destruction of β cells seen in type 1 diabetes in humans. The deficiency of the LDL receptor results in lipoprotein profiles that resemble human profiles (LDL and very low density lipoprotein [VLDL] enriched), which promotes atherosclerosis formation and progression. Importantly, advanced lesions with a disrupted phenotype are formed in the brachiocephalic artery (BCA) of these mice [12]. The BCA is a well-defined artery characterized by turbulent patterns of blood flow, which lead to formation of advanced plaques that reproducibly present with intraplaque hemorrhage [9]. The lesions at this site also exhibit other features characteristic of unstable human lesions, including thinning fibrous cap, necrotic core formation, calcification, and the presence of inflammatory cells [9]. We have shown that in the $LDLR^{-/-}$;GP model, diabetes accelerates lesion initiation, measured as an increased macrophage accumulation and fatty streak formation in the BCA [12]. 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. Accordingly, intense insulin therapy normalized the diabetes-accelerated lesion initiation, thus confirming that the accelerated lesion initiation was an effect of suboptimal metabolic control. However, in the setting of severe dyslipidemia, the effects of diabetes on atherosclerosis were masked [2,12].

Our laboratory recently conducted a study using the $LDLR^{-/-}$;GP model to investigate the effect diabetes has on advanced, clinically more relevant lesions [8••]. The study's initial phase allowed advanced atherosclerotic lesions to form, and diabetes was induced after lesions developed into complex lesions with necrotic cores, fibrous caps, and beginning evidence of calcification. In this study, the effects of diabetes on advance lesions, without confounding effects on lesion initiation, could therefore be investigated. Diabetes did not result in changes in lesion size but significantly increased the presence of intraplaque hemorrhage and disruption of advanced BCA lesions [8••]. This suggests that diabetes can promote disruption of advanced lesions, potentially mimicking the process leading to cardiovascular-related events in humans with diabetes.

Is diabetes-induced plaque disruption due to glucose or lipids? Using a helper-dependent adenovirus we stably overexpressed the murine VLDL receptor in the liver of these mice, which markedly reduced VLDL and LDL levels in diabetic and nondiabetic mice without reducing hyperglycemia [8••]. Strikingly, aggressive lipid lowering corrected the appearance of intraplaque hemorrhage in diabetic mice, suggesting that VLDL/LDL are required for diabetes-induced plaque disruption, and that hyperglycemia alone is insufficient [8••]. Thus, our results identify VLDL/LDL as the culprit in disruption of lesions in type 1 diabetic mice, even though VLDL/LDL levels are not markedly affected by type 1 diabetes [12]. In early stages of lesion development, conversely, hyperglycemia is likely to promote lesion initiation [12].

The results of the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study suggest that strict blood glucose control has long-lasting benefits associated with reduced cardiovascular events in patients with type 1 diabetes years after the treatment period [4]. This phenomenon has been termed "metabolic memory." One possible explanation is that hyperglycemia may impact endothelial function early in lesion initiation, and that this could result in increased cardiovascular events years later. Hyperglycemia's effects may be less prominent in advanced lesions and in patients with hyperlipidemia. This hypothesis is consistent with the findings that intense blood glucose control does not significantly reduce cardiovascular-related events in type 2 diabetes, which is associated with hyperlipidemia that is likely to override hyperglycemia's relatively minor effects. This theory would suggest a greater need to focus on strict glucose control early in type 1 diabetes to reduce cardiovascular mortality, and additionally to focus on aggressive lipid lowering in type 2 diabetes and in later stages of type 1 diabetes. However, we would like to emphasize that hyperglycemia may promote thrombosis or other processes involved in cardiovascular events downstream of plaque disruption that are not well mimicked by the animal models currently available. Therefore, new animal models are urgently needed.

The Contributions of Glucose and Lipids Are Difficult to Distinguish

Prolonged hyperglycemia is often suggested to be the primary cause of diabetic complications, and thus has been the focus of most theories explaining the increase in macrovascular

disorders in diabetes. The mechanisms whereby elevated glucose might contribute to vascular disease include increased shunting of glucose to the aldose reductase (AR) pathway, irreversible protein glycation, activation of protein kinase C (PKC), and increased oxidation. These pathways have been reviewed extensively elsewhere [13] and are briefly summarized below. Even though ample in vitro evidence supports the existence of negative effects of high glucose concentrations through these pathways, in many cases it is difficult to differentiate between negative effects of glucose versus lipids in vivo. Furthermore, many studies are performed in cultured cells, and it remains unclear which mechanisms contribute to the development of advanced lesions.

The AR pathway

Compelling evidence that hyperglycemia is likely to contribute to diabetes-accelerated atherosclerosis comes from the AR studies by Vikramadithyan et al. [14]. AR catalyzes the reduction of glucose to sorbitol, the rate-limiting step in the polyol pathway. In the setting of hyperglycemia, glucose can shunt into this pathway. The polyol pathway has been suggested as a prominent source of oxidative stress in diabetes. Several clinical trials using AR inhibitors have been disappointing, yet some trials suggest benefits [14]. To determine the effect of human levels of AR in diabetes-accelerated atherosclerosis, human AR was expressed in $LDLR^{-/-}$ AR-transgenic mice. AR expression alone did not affect atherosclerosis; however, AR significantly augmented diabetes-accelerated atherosclerosis without affecting lipid profiles [14]. This suggests that hyperglycemia, not hyperlipidemia, promotes atherosclerosis through increased glucose metabolism by the polyol pathway. However, AR also acts on certain phospholipids. Therefore, the effects of glucose and lipids on atherosclerosis may not be separable even when the AR pathway is analyzed. Furthermore, it remains to be studied what, if any, effects AR may have on lesion disruption.

Advanced glycation/lipoxidation end products

Hyperglycemia appears to have irreversible long-term effects, which has led to the theory of metabolic memory. As discussed above, this is exemplified by the long-term benefits of early intense insulin therapy on cardiovascular-related events in humans with type 1 diabetes [4]. One hypothesis is that metabolic memory is due to the formation of irreversible advanced glycation end products (AGEs). These are formed and accumulate during prolonged exposure to hyperglycemia, and persist despite correction of hyperglycemia. Consequences of AGE formation can include impaired protein function, modification of extracellular matrix, and impaired cellular signaling [13]. AGEs are present in human atherosclerotic lesions and are increased in serum in type 1 and type 2 diabetes [15,16]. The process of advanced glycation can also involve lipids, seen by the generation of advanced lipoxidation end products, which have been shown to increase expression of proinflammatory genes and increase monocyte adhesion to endothelial cells [17].

AGEs can also elicit their effects through interaction with several different receptors. The most notable AGE receptor is the receptor for AGE (RAGE), and RAGE-AGE interactions and subsequent signaling have been the longstanding theory for some of AGEs' negative impact in diabetes [18,19•,20]. RAGE is present on all vascular cells, including macrophages, and interaction with RAGE induces an increase in adhesion molecule expression and increased inflammation. RAGE signaling is believed to be involved in diabetes-accelerated atherosclerosis because RAGE deficiency or blocking inhibits diabetes-accelerated atherosclerosis in animal models [18]. However, in the same atherosclerosis models, RAGE deficiency attenuates atherosclerosis progression also under nondiabetic conditions, showing that RAGE signaling constitutes a more general pathway involved in disease processes and is not specific to diabetes [19•]. RAGE binds several ligands in addition to AGEs. Blocking RAGE results in inhibition of both lesion size and complexity in established atherosclerotic lesions [20]. It remains to be determined to what extent RAGE signaling is augmented by hyperglycemia, or if diabetes is augmenting a yet-unidentified factor that promotes RAGE signaling in atherosclerotic lesions.

Diacylglycerol-PKC activation

Another mechanism proposed to explain glucose's negative effects is the diacylglycerol (DAG)-PKC activation pathway [21]. This theory exemplifies how glucose can function through lipid intermediates, again making it difficult to distinguish the effects of glucose from those of lipids. High glucose can increase DAG through de novo synthesis or through phospholipase D activation. Activation of PKC can affect blood flow, result in thickening of the basement membrane and expansion of extracellular matrix, and can promote vascular permeability and cell growth. Many of these mechanisms have been studied in relation to microvascular complications, but it is likely that they also play a role in macrovascular complications. Endothelial dysfunction is a common theme in diabetes-related macrovascular complications, and PKC activation may exacerbate endothelial dysfunction through increasing permeability, decreasing nitric oxide availability, and increasing oxidative stress. Recently, activation of PKC-α and PKC-δ has been implicated in the glucose-stimulated increase in toll-like receptor (TLR)-2 and -4 in monocytes [22]. However, PKC's potential role in advanced stages of atherosclerosis remains unclear, as does whether PKC inhibition is a viable option in treating atherosclerosis at clinically relevant stages.

Oxidation

Many theories proposed to explain the mechanisms of atherosclerosis include oxidative stress, which is believed

to be exaggerated in diabetes settings. Increased oxidative damage is suspected to occur directly from hyperglycemia, such as through overproduction of superoxide, or indirectly through AGEs, PKC activation, and the hexosamine pathway [13]. Increased oxidative stress is proposed to increase lipid uptake by macrophages, induce inflammation, and promote endothelial dysfunction [23]. A study conducted by Pennathur et al. [24] in type 1 diabetic nonhuman primates investigated the evidence for local oxidation in the atherosclerotic vascular wall. The findings indicate that formation of hydroxyl radicals and related species is responsible for most of the protein oxidation products in diabetes. However, this study was limited to early stages of lesion development, and most of the potential mechanism related to oxidation is focused on endothelial dysfunction and foam cell formation. The oxidation theory of atherosclerosis suggests that any disease process that promotes oxidation should increase atherosclerosis. However, disappointing results from both clinical trials and animal models of advanced atherosclerosis using antioxidants suggest the oxidation theory should be revisited [25]. Diabetes may increase localized oxidation within the arterial wall, and this may be a factor in initiating lesions. However, hyperlipidemia is also expected to play a role in oxidation events, and it remains unclear the potential for oxidation, and thus antioxidant therapies, to affect advanced lesions.

The Role of Glucose and Lipids in Inflammation Promoted by Diabetes

Atherosclerosis is an inflammatory disease, and both type 1 and type 2 diabetes appear to promote an altered inflammatory profile. Many studies have shown that glucose and lipids can modulate inflammatory mediators, and this may be a potential mechanism of diabetes-accelerated atherosclerosis. Exciting discoveries over the past few years in monocyte/macrophage biology will direct new investigations and offer new possibilities in diabetes-related complications.

Monocyte and endothelial cell interaction

The interaction between monocytes and endothelial cells is an initiating event in atherosclerosis. A large body of in vitro evidence supports the theory that hyperglycemia can promote endothelial dysfunction, and this may be the underlying mechanism of type 1 diabetes-accelerated atherosclerosis [26]. Hyperglycemia has been suggested to activate endothelial cells, as well as to upregulate vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1 mRNA and protein [27]. Interestingly, endothelial RAGE can act as an adhesion receptor by binding leukocyte β_2 integrins [2]. RAGE induction might therefore serve as an additional pathway to increase monocyte-endothelial adhesion in diabetes. This data suggests that hyperglycemia can promote both recruitment and adhesion of monocytes to the endothelial layer. However, it is unknown in what stage of lesion development these events play the most important role. Our data on mice with type 1 diabetes would suggest that monocyte-endothelial interactions promoted by diabetes might be most important in lesion initiation and early fatty streak formation. Recent data in diabetic rats determined that fluctuations in blood glucose increased monocyte adhesion to the endothelium [28]. It remains to be identified to what extent increased monocyte adherence to the endothelium is associated with lesion disruption.

Monocyte/macrophage phenotypes

Type 1 diabetes has been reported to promote an inflammatory phenotype in circulating monocytes, characterized by increased levels of CD11b, interleukin-6, TLR2, and TLR4 [29,30]. The increase in TLR levels correlated with the release of proinflammatory cytokines, and in vitro analysis indicated that high glucose may be responsible for the increased TLR surface expression [22,30]. Although the generality of these interesting observations remain to be established, a proinflammatory phenotype in monocytes is also observed in type 2 diabetes [31]. Monocyte recruitment to the artery wall is a main event in lesion development. The findings that diabetes can promote a proinflammatory monocyte phenotype suggest that diabetes could enhance the recruitment of monocytes and promote vascular inflammation, further accelerating atherosclerosis. Our studies and others have demonstrated that hyperlipidemia may mask the effects of hyperglycemia on atherosclerotic lesions [2]. One potential reason for this is hyperlipidemia's recently demonstrated effect on circulating monocyte subsets. Different monocyte populations that express different inflammatory mediators and are believed to affect the progression of atherosclerosis are found in humans and mice. In humans, these monocytes are characterized by the expression of several cell surface markers and are divided into $CD14^{+}CD16^{-}CCR2^{+}CX3CR1^{-}$ and $CD14^{lo}CD116^{+}CCR2^{-}CX3CR1^{+}$ populations [32]. The $CD14^{high}$ populations of monocytes are involved in acute inflammation and are recruited to inflammation sites. Mice also have similar monocyte populations with expected similar phenotypes—the $Ly6C^{+}CCR2^{+}CX3CR1^{-}$ and $Ly6C^{-}CCR2^{-}CX3CR1^{+}$ populations, respectively. Recently, very intriguing results have shown that the $Ly6C^{high}$ population is increased in the circulation of apolipoprotein E–deficient (apo $E^{-/-}$) mice on a high-fat diet [33,34]. The most interesting finding demonstrated that the $Ly6C^{high}$ population preferentially migrated into atherosclerotic lesions [34]. The effect of diabetes on these monocyte subsets has not been fully investigated. Human studies suggest that diabetes does not change the populations of monocytes, yet there does appear to be a shift in the inflammatory phenotype of monocytes [35].

In addition to the effects of diabetes on circulating monocytes, our observations suggest that type 1 diabetes promotes a specific phenotype in macrophages, associated with an increase in the inflammatory molecule S100A9, and that these macrophages may promote intraplaque hemorrhage [8••]. It is intriguing to speculate that different monocyte/macrophage phenotypes may contribute to a more unstable plaque phenotype in diabetes. Further investigation is needed to identify potential subtle changes in monocytes/macrophages, and also to determine the possible contribution of these cell populations on atherosclerosis and other complications of diabetes, such as impaired wound healing.

Adipose tissue, inflammation, and type 2 diabetes

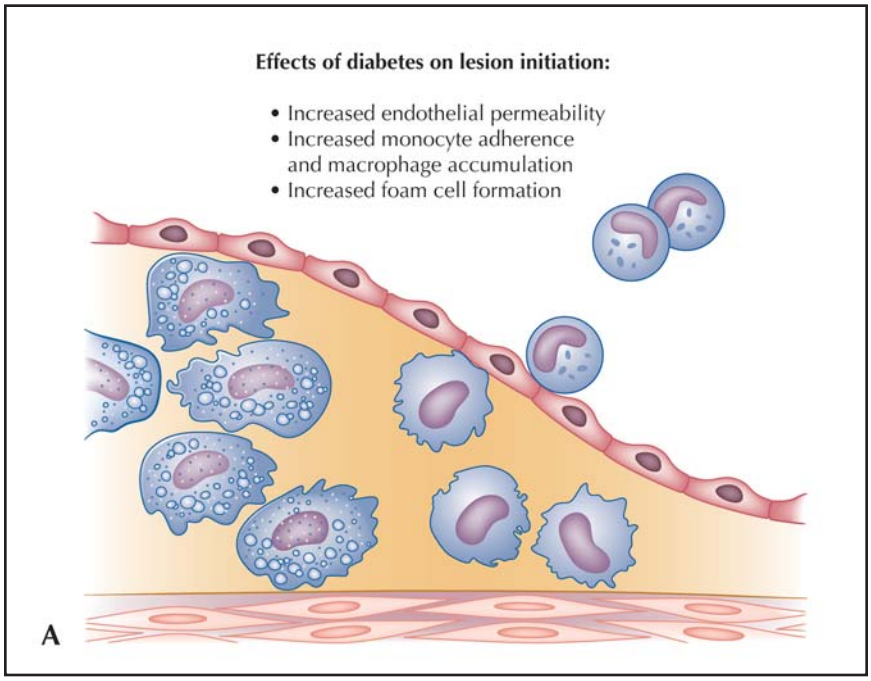
Type 2 diabetes is often associated with obesity, and both disorders lead to an increased risk for acute myocardial ischemic syndromes [36]. This association is not coincidental—evidence suggests that obesity precedes insulin resistance and can result in the release of factors that promote lesion development. The lipocentric theory of the pathogenesis of type 2 diabetes suggests that ectopic lipid deposition promotes dysregulation of fatty acid metabolism, which in turn induces insulin resistance [5]. Obesity increases cardiovascular disease risk, and inflamed adipose tissue appears to promote lesion progression [37]. This suggests it is necessary to investigate the effects of obesity and adipose tissue in addition to traditional changes in metabolic control to appropriately determine the risk of atherosclerosis in type 2 diabetes.

Adipose tissue releases adipokines and adipocyte-derived hormones that may have specific cellular effects that mediate insulin resistance and atherosclerosis. Adiponectin levels inversely correlate with insulin resistance, atherosclerosis, and obesity [38]. Overexpression of adiponectin is atheroprotective in apo $E^{-/-}$ mice and rabbits, both of which show a reduction in lesion area, adhesion molecule expression, and foam cell formation [39,40]. Further studies suggest adiponectin may act locally, potentially by reducing foam cell formation, and that adiponectin may affect plasma triglyceride levels through increased VLDL-triglyceride catabolism [40–43]. Accordingly, a reduction in adiponectin levels augments insulin resistance and hyperglycemia, promoting a cycle of enhanced diabetes and lesion development [44]. Leptin is an adipose tissue–derived hormone that potentially opposes adiponectin's actions. Leptin levels are elevated in obesity, and evidence suggests leptin is proatherogenic [45]. Interestingly, leptin may promote a more advanced lesion phenotype, suggesting levels of adipocyte-derived factors may be important targets during the more advanced stages of atherosclerosis [46]. The ratio between adiponectin and leptin may thus regulate the development of type 2 diabetes and atherogenic risk.

Macrophages in adipose tissue have distinct phenotypes in obese and nonobese mice [47]. Macrophages respond to inflammatory signals released from adipocytes, in addition to high fatty acid levels associated with obesity, which in turn stimulate macrophages to release proinflammatory cytokines [48]. It appears that the macrophages in adipose tissue in obese mice phenotypically are classically activated (also known as M1 polarization), compared with macrophages in lean mice that display characteristics of alternative activation (M2 polarization) [49••]. Recent research showed that transplanting inflamed adipose tissue into apo $E^{-/-}$ led to increased inflammation and atherosclerosis, supporting the theory that adipose-derived inflammation promotes atherosclerosis [37]. This suggests that inflammation is a central mediator involved in obesity and atherosclerosis. The fact that these factors are at play before diagnosis of type 2 diabetes complicates the identification of specific factors that affect lesion progression in type 2 diabetes. Recent interesting data show that peroxisome proliferator-activated receptor (PPAR)-γ promotes formation of a more alternatively active macrophage phenotype, and increases adiponectin levels and other antiatherosclerotic factors, suggesting PPAR-γ agonists may have beneficial effects in diabetes and obesity-accelerated atherosclerosis [50].

Conclusions

Both type 1 and type 2 diabetes increase the risk of cardiovascular events, likely due to accelerated formation of atherosclerotic lesions and disruption of advanced atherosclerotic plaques. The specific roles of glucose and lipids in atherosclerosis in the diabetes setting are less clear, they may not be entirely distinguishable, and they appear to be different in type 1 and type 2 diabetes. This article summarized the potential impact of diabetes on different phases of atherosclerosis (Fig. 1), proposing that glucose and lipids may have different effects at specific time points in the course of lesion development. Furthermore, even though hyperglycemia is common in diabetes, it is not clear that hyperglycemia plays a significant role in the final disruption of the atherosclerotic plaque. Therefore, therapies need to accommodate for the expected stage of atherosclerosis. Furthermore, the concept of metabolic memory may apply to the time course of atherosclerotic lesion formation. It is possible that poor glucose control early in lesion development may lead to increased cardiovascular events years later, further supporting the idea that therapies should have specific focus on early glucose control in patients with type 1 diabetes. This, however, is likely a less important focus in type 2 diabetes, in which lipid abnormalities and obesity-related inflammation are in place before the onset of diabetes/hyperglycemia. These factors may be the driving force of accelerated atherosclerosis associated with type 2 diabetes and could potentially mask any additive effect of hyperglycemia.



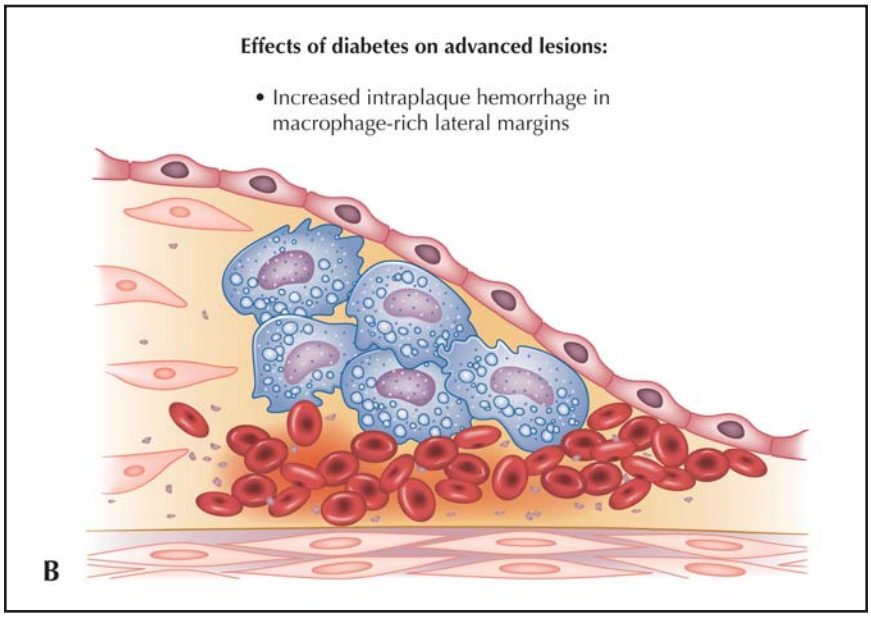


Figure 1. Effects of type 1 diabetes throughout the progression of a murine atherosclerotic lesion. **A,** During initiation, hyperglycemia may promote endothelial dysfunction and monocyte adherence, and increase levels of oxidation that might promote macrophage foam cell formation. **B,** As the lesions progress, evidence suggests that diabetic lesions have increased intraplaque hemorrhage. In this figure, the lesion is covered by an endothelial cell layer. Medium-sized round cells outside the lesion represent monocytes and the large globular cells in the lesion represent macrophages. Lesion macrophages with intracellular round light droplets represent foam cells. The elongated cells in the lesion represent smooth muscle cells, small round cells are red blood cells, and other small nonspecific shapes indicate dead cell debris.

Inflammation has long been recognized to be associated with atherosclerosis progression, and research supports the existence of an increased inflammatory state in diabetes. New research identifies specific phenotypes in monocyte/macrophages that may present intriguing areas of research in the fields of diabetes and atherosclerosis. Many questions remain to be investigated, including the theory that accelerated lesion initiation can lead to subsequent accelerated lesion disruption, and whether or not hyperglycemia is directly involved in promoting lesion disruption. Inflammatory monocyte and/or macrophage subsets in diabetes, and their relation to atherosclerosis, need further study. In type 2 diabetes, the roles of adipose-derived factors and inflammation, lipid abnormalities, as well as the extent of pre-existing atherosclerosis, are likely to be important considerations in the development of therapies to reduce cardiovascular events.

Disclosures

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Ruderman NB, Haudenschild C: **Diabetes as an atherogenic factor.** *Prog Cardiovasc Dis* 1984, **26:**373–412.
2. Kanter JE, Johansson F, LeBoeuf RC, Bornfeldt KE: **Do glucose and lipids exert independent effects on atherosclerotic lesion initiation or progression to advanced plaques?** *Circ Res* 2007, **100:**769–781.
3. **The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group [no authors listed].** *N Engl J Med* 1993, **329:**977–986.
4. **Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group [no authors listed].** *N Engl J Med* 2005, **353:**2643–2653.
5. McGarry JD: **Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes.** *Diabetes* 2002, **51:**7–18.
6. **Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The ADVANCE Collaborative Group [no authors listed].** *N Engl J Med* 2008, **358:**2560–2572.
7. **Effects of intensive glucose lowering in type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes Study Group [no authors listed].** *N Engl J Med* 2008, **358:**2545–2559.
8. •• Johansson F, Kramer F, Barnhart S, et al.: **Type 1 diabetes promotes disruption of advanced atherosclerotic lesions in LDL receptor-deficient mice.** *Proc Natl Acad Sci U S A* 2008, **105:**2082–2087.

Shows that diabetes promotes disruption and intraplaque hemorrhage independently of effects on lesion initiation in a mouse model.

9. Rosenfeld ME, Averill MM, Bennett BJ, Schwartz SM: **Progression and disruption of advanced atherosclerotic plaques in murine models.** *Curr Drug Targets* 2008, **9:**210–216.
10. Virmani R, Burke AP, Farb A, Kolodgie FD: **Pathology of the vulnerable plaque.** *J Am Coll Cardiol* 2006, **47(8 Suppl):** C13–C18.
11. Gerrity RG, Natarajan R, Nadler JL, Kimsey T: **Diabetes-induced accelerated atherosclerosis in swine.** *Diabetes* 2001, **50:**1654–1665.
12. Renard CB, Kramer F, Johansson F, et al.: **Diabetes and diabetes-associated lipid abnormalities have distinct effects on initiation and progression of atherosclerotic lesions.** *J Clin Invest* 2004, **114:**659–668.
13. Aronson D: **Hyperglycemia and the pathobiology of diabetic complications.** *Adv Cardiol* 2008, **45:**1–16.
14. Vikramadithyan RK, Hu Y, Noh HL, et al.: **Human aldose reductase expression accelerates diabetic atherosclerosis in transgenic mice.** *J Clin Invest* 2005, **115:**2434–2443.
15. Nakamura Y, Horii Y, Nishino T, et al.: **Immunohistochemical localization of advanced glycosylation end products in coronary atheroma and cardiac tissue in diabetes mellitus.** *Am J Pathol* 1993, **143:**1649–1656.
16. Kalousova M, Skrha J, Zima T: **Advanced glycation end-products and advanced oxidation protein products in patients with diabetes mellitus.** *Physiol Res* 2002, **51:**597–604.
17. Shanmugam N, Figarola JL, Li Y, et al.: **Proinflammatory effects of advanced lipoxidation end products in monocytes.** *Diabetes* 2008, **57:**879–888.
18. Soro-Paavonen A, Watson AM, Li J, et al.: **RAGE deficiency attenuates the development of atherosclerosis in diabetes.** *Diabetes* 2008, **57:**2461–2469.
19. • Harja E, Bu DX, Hudson BI, et al.: **Vascular and inflammatory stresses mediate atherosclerosis via RAGE and its ligands in apoE-/- mice.** *J Clin Invest* 2008, **118:**183–194.

Provides evidence that RAGE effects on atherosclerosis are not specific to diabetes.

20. Bucciarelli LG, Wendt T, Qu W, et al.: **RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice.** *Circulation* 2002, **106:**2827–2835.
21. Das Evcimen N, King GL: **The role of protein kinase C activation and the vascular complications of diabetes.** *Pharmacol Res* 2007, **55:**498–510.
22. Dasu MR, Devaraj S, Ling Z, et al.: **High glucose induces toll-like receptor expression in human monocytes: mechanism of activation.** *Diabetes* 2008, **57:**3090–3098.
23. Newsholme P, Haber EP, Hirabara SM, et al.: **Diabetes associated cell stress and dysfunction: role of mitochondrial and non-mitochondrial ROS production and activity.** *J Physiol* 2007, **583:**9–24.
24. Pennathur S, Wagner JD, Leeuwenburgh C, et al.: **A hydroxyl radical-like species oxidizes cynomolgus monkey artery wall proteins in early diabetic vascular disease.** *J Clin Invest* 2001, **107:**853–860.
25. Averill MM, Bennett BJ, Rattazzi M, et al.: **Neither antioxidants nor genistein inhibit the progression of established atherosclerotic lesions in older apoE deficient mice.** *Atherosclerosis* 2008 Jul 1 (Epub ahead of print).
26. Nakagami H, Kaneda Y, Ogihara T, Morishita R: **Endothelial dysfunction in hyperglycemia as a trigger of atherosclerosis.** *Curr Diab Rev* 2005, **1:**59–63.
27. Piga R, Naito Y, Kokura S, et al.: **Short-term high glucose exposure induces monocyte-endothelial cells adhesion and transmigration by increasing VCAM-1 and MCP-1 expression in human aortic endothelial cells.** *Atherosclerosis* 2007, **193:**328–334.
28. Watada H, Azuma K, Kawamori R: **Glucose fluctuation on the progression of diabetic macroangiopathy: new findings from monocyte adhesion to endothelial cells.** *Diabetes Res Clin Pract* 2007, **77:**S58–S61.
29. Devaraj S, Glaser N, Griffen S, et al.: **Increased monocytic activity and biomarkers of inflammation in patients with type 1 diabetes.** *Diabetes* 2006, **55:**774–779.
30. Devaraj S, Dasu MR, Rockwood J, et al.: **Increased toll-like receptor (TLR) 2 and TLR4 expression in monocytes from patients with type 1 diabetes: further evidence of a proinflammatory state.** *J Clin Endocrinol Metab* 2008, **93:**578–583.
31. Mazzone T, Chait A, Plutzky J: **Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies.** *Lancet* 2008, **371:**1800–1809.
32. Gordon S, Taylor PR: **Monocyte and macrophage heterogeneity.** *Nat Rev Immunol* 2005, **5:**953–964.
33. Swirski FK, Libby P, Aikawa E, et al.: **Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata.** *J Clin Invest* 2007, **117:**195–205.
34. Tacke F, Alvarez D, Kaplan TJ, et al.: **Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques.** *J Clin Invest* 2007, **117:**185–194.
35. Patiño R, Ibarra J, Rodriguez A, et al.: **Circulating monocytes in patients with diabetes mellitus, arterial disease, and increased CD14 expression.** *Am J Cardiol* 2000, **85:**1288–1291.
36. Zaliunas R, Slapikas R, Babarskiene R, et al.: **The prevalence of the metabolic syndrome components and their combinations in men and women with acute ischemic syndromes.** *Medicina (Kaunas)* 2008, **44:**521–528.

37. Ohman MK, Shen Y, Obimba CI, et al.: **Visceral adipose tissue inflammation accelerates atherosclerosis in apolipoprotein E-deficient mice.** *Circulation* 2008, **117:**798–805.
38. Beltowski J, Jamroz-Wisniewska A, Widomska S: **Adiponectin and its role in cardiovascular diseases.** *Cardiovasc Hematol Disord Drug Targets* 2008, **8:**7–46.
39. Okamoto Y, Kihara S, Ouchi N, et al.: **Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice.** *Circulation* 2002, **106:**2767–2770.
40. Li CJ, Sun HW, Zhu FL, et al.: **Local adiponectin treatment reduces atherosclerotic plaque size in rabbits.** *J Endocrinol* 2007, **193:**137–145.
41. Tsubakio-Yamamoto K, Matsuura F, Koseki M, et al.: **Adiponectin prevents atherosclerosis by increasing cholesterol efflux from macrophages.** *Biochem Biophys Res Commun* 2008, **375:**390–394.
42. Tian L, Luo N, Klein RL, et al.: **Adiponectin reduces lipid accumulation in macrophage foam cells.** *Atherosclerosis* 2008 Apr 20 (Epub ahead of print).
43. Qiao L, Zou C, van der Westhuyzen DR, Shao J: **Adiponectin reduces plasma triglyceride by increasing VLDL triglyceride catabolism.** *Diabetes* 2008, **57:**1824–1833.
44. Sheng T, Yang K: **Adiponectin and its association with insulin resistance and type 2 diabetes.** *J Genet Genomics* 2008, **35:**321–326.
45. Dubey L, Hesong Z: **Role of leptin in atherogenesis.** *Exp Clin Cardol* 2006, **11:**269–275.
46. Chiba T, Shinozaki S, Nakazawa T, et al.: **Leptin deficiency suppresses progression of atherosclerosis in apoE-deficient mice.** *Atherosclerosis* 2008, **196:**68–75.
47. Lumeng CN, Bodzin JL, Saltiel AR: **Obesity induces a phenotypic switch in adipose tissue macrophage polarization.** *J Clin Invest* 2007, **117:**175–184.
48. Suganami T, Tanimoto-Koyama K, Nishida J, et al.: **Role of the Toll-like receptor 4/NF-kappaB pathway in saturated fatty acid-induced inflammatory changes in the interaction between adipocytes and macrophages.** *Arterioscler Thromb Vasc Biol* 2007, **27:**84–91.
49.•• Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, et al.: **Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance.** *Nature* 2007, **447:**1116–1120.
Demonstrates that macrophage polarization affects diet-induced obesity and insulin resistance in a mouse model.
50. Duan SZ, Usher MG, Mortensen RM: **Peroxisome proliferator-activated receptor-gamma-mediated effects in the vasculature.** *Circ Res* 2008, **102:**283–294.