

## Impact of Diabetes Mellitus

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The global prevalence of diabetes mellitus among adults has risen from 4.7% in 1980 to 8.5% in 2014, increasing the number of adults with diabetes mellitus to a staggering 422 million worldwide, according to the World Health Organization. For comparison, this number is larger than the total population of the United States. Diabetes mellitus not only reduces quality of life and life expectancy, but is also a major cause of several microvascular complications and macrovascular complications that lead to blindness, renal failure, myocardial infarction, stroke, and the necessity to amputate limbs. The burden of diabetes mellitus-associated complications worldwide is therefore a major healthcare problem that we urgently need to find solutions to. In this context, a large body of research has been devoted to identifying risk factors of vascular complications of diabetes mellitus with the goal of improving prevention of these complications. Such research has revealed that vascular complications of diabetes mellitus are associated with multiple risk factors—including dyslipidemia, hypertension, smoking, age, metabolic control, and systemic inflammation—and that the relative contribution of these risk factors is likely to vary depending on the type of diabetes mellitus and what risk factors are present in a given subject. Other research is aimed at finding novel and reliable biomarkers for vascular complications of diabetes mellitus and novel targets for treatment. In this review, we highlight manuscripts published in *ATVB* within the past 2 years, focusing on novel pathways that might contribute to vascular complications of diabetes mellitus. This work ranges from experiments on isolated cells to animal models of diabetes mellitus to studies in humans.

### Novel Pathways for Vascular Cell Perturbations in Diabetes Mellitus

Elevated blood glucose is a hallmark of all types of diabetes mellitus, which include type 1 diabetes mellitus, type 2 diabetes mellitus, diabetes mellitus characterized by aspects of both type 1 and type 2 diabetes mellitus, gestational diabetes mellitus (GDM), and rare cases of diabetes mellitus caused by, for example, pancreatic trauma. Increased levels of circulating glucose have been proposed to mediate many of the

deleterious cellular effects of diabetes mellitus, especially in endothelial cells.<sup>1</sup> It is well established that diabetes mellitus leads to reduced vasodilation in response to acetylcholine.<sup>2–4</sup> This effect is believed to be mediated by a reduced action and production of nitric oxide by endothelial nitric oxide synthase (eNOS). A meta-analysis of 39 studies of acute blood glucose elevation recently published in *ATVB* demonstrated that acute glucose elevation indeed impairs endothelial function (vasodilation) in healthy subjects and subjects with cardiometabolic disease.<sup>5</sup> Interestingly, although the endothelial cell response was negatively impacted by acute hyperglycemia, smooth muscle function appeared to be preserved during acute hyperglycemia. These findings suggest that macrovascular endothelial cells might be particularly sensitive to the extracellular glucose environment, at least as compared with arterial smooth muscle cells (SMCs). It is not known to what extent acute blood glucose elevation has direct effects on endothelial cells in vivo and if the effect is primarily mediated by secondary mechanisms. In the meta-analysis above, macrovascular endothelial function was inversely associated with age, blood pressure, and low-density lipoprotein cholesterol. Addressing the relative contribution of different factors associated with endothelial cell dysfunction in humans, Walther et al showed in a cross-sectional study that the presence of metabolic syndrome resulted in depressed vascular endothelial function and nitric oxide responses in both microvascular and macrovascular beds. Furthermore, type 2 diabetes mellitus in combination with metabolic syndrome further augmented SMC dysfunction. Subjects with metabolic syndrome in this study exhibited elevated body mass index, fat mass, blood pressure, fasting glucose, glycohemoglobin, insulin, insulin resistance, triglycerides and inflammatory markers, and reduced high-density lipoprotein (HDL) cholesterol. The type 2 diabetic group had higher fasting glucose, glycohemoglobin, insulin and insulin resistance, and increased waist circumference, as compared with the metabolic syndrome group of subjects without diabetes mellitus. Central adiposity, rather than changes in blood glucose, was found to be a predictor for this exacerbated vascular phenotype.<sup>6</sup> These 2 studies highlight the impact of diabetes mellitus on vascular cells in humans and suggest that these cells are responsive to extracellular perturbations associated with the diabetic environment and that hyperglycemia is unlikely to be solely responsible for vascular dysfunction associated with diabetes mellitus.

What are some of the intracellular mechanisms resulting in vascular dysfunction in diabetes mellitus? Several recent studies published in *ATVB* have investigated this interesting topic. These studies point to novel roles of microRNAs (miRNAs) in endothelial cells and arterial SMCs, the importance of tissue context for cellular responses, and a heretofore

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unknown role for adipose tissue in modulating endothelial cell responses in humans. Several of these studies used endothelial cells isolated from human subjects to investigate effects of diabetes mellitus, which makes them particularly relevant to understand factors that might contribute to vascular complications in patients with diabetes mellitus.

miRNAs are short (usually 18–24 nucleotides in length) noncoding RNAs that mainly act as post-transcriptional repressors. They interact with the 3'-untranslated region of messenger RNAs and degrade the target mRNA or suppress its translation. Several miRs have been implicated in endothelial dysfunction.<sup>7</sup> To investigate how diabetes mellitus affects endothelial function and miRs in human endothelial cells, Floris et al took the approach of isolating human umbilical vein endothelial cells (HUVECs) from umbilical cords from pregnancies that were complicated by GDM and from healthy control pregnancies.<sup>8</sup> The use of HUVECs from diabetics and nondiabetics is a clever approach to allow studies of diabetes mellitus on freshly isolated human endothelial cells, although it is possible that HUVECs exhibit some differences vis-à-vis endothelial cells involved in vascular complications of diabetes mellitus. The authors demonstrated that HUVECs isolated from GDM-complicated pregnancies exhibit increased apoptosis and a reduced ability to form capillary networks, as compared with HUVECs from healthy controls. GDM was associated with increased HUVEC levels of miR101 and reduced Enhancer of Zester Homolog-2 (EZH2) levels. EZH2 is a histone methyltransferase involved in gene silencing, and the authors showed that EZH2 directly binds to the miR101 promoter region and that GDM is associated with reduced EZH2 binding, thus allowing for increased levels of miR101 to accumulate under these conditions. Restoring EZH2 levels in GDM HUVECs restored some of functional deficiencies associated with GDM. The authors further showed that the effects of GDM on miR101 and EZH2 binding could be reproduced by culturing normal HUVECs under high glucose conditions, suggesting a potential direct role for glucose in mediating the changes in this pathway.

miRNAs have been implicated not only in endothelial cell responses to the diabetic environment, but also in SMC dysfunction in diabetes mellitus.<sup>9</sup> Reddy et al showed that 135 miRNAs were differentially regulated in SMC cultured from thoracic aortas from diabetic db/db mice as compared with SMC cultured from nondiabetic db/+ controls. The diabetes mellitus-induced increases in miR504 levels were further validated, and overexpression of miR504 was demonstrated to stimulate proliferation and migration of SMC. Again, the effect of diabetes mellitus on miR504 induction was mimicked by exposure of cultured SMCs to high glucose, suggesting that this effect of diabetes mellitus might be mediated by a direct effect of elevated glucose. Because the effect of diabetes mellitus was maintained in culture, it is possible that the diabetes mellitus effect on these SMCs is because of genetic differences or epigenetic changes, which are known to occur in the vascular wall.<sup>10</sup> These findings will have to be verified in the human setting. In addition, plasma levels of other miRs, in particular miR-191 and miR-200b, have been shown to be altered in human subjects with type 2 diabetes mellitus and in subjects with type 2 diabetes mellitus and peripheral arterial

disease and chronic wounds.<sup>11</sup> Together, these studies suggest that diabetes mellitus results in altered levels of miRNAs both systemically and in vascular cells. These changes are likely to contribute to vascular dysfunction associated with diabetes mellitus.

Bretón-Romero et al described another novel pathway for endothelial dysfunction associated with type 2 diabetes mellitus in humans.<sup>12</sup> These authors used primary endothelial cells obtained by dislodging and harvesting superficial forearm vein endothelial cells from subjects with type 2 diabetes mellitus and controls without diabetes mellitus. The studies demonstrated that wingless-type family member 5a and activation of JNK mediate impairment of eNOS and reduced nitric oxide production, resulting in impaired vasodilation. The authors concluded that wingless-type family member 5a acted through JNK, but not via increased levels of reactive oxygen species, to inhibit eNOS and flow-mediated dilation. The strength of Bretón-Romero's study is the use of primary human endothelial cells from subjects with diabetes mellitus and controls.

Recent studies have also investigated the role of adipose tissue in affecting vascular responses. In a study using primary human cells, Karki et al showed that endothelial cells from the visceral adipose tissue, but not from subcutaneous adipose tissue, became insensitive to insulin-stimulated eNOS phosphorylation/activation in obese subjects, whereas visceral adipose tissue insulin signaling was intact in healthy subjects.<sup>13</sup> Subjects in the obese group had higher body mass index (43 kg/m<sup>2</sup>), elevated levels of glycohemoglobin (HbA1c), increased measures of insulin resistance, and presence of diabetes mellitus, as compared with the lean control group. The authors then continued to demonstrate a causal role for Forkhead Box O1 (FOXO-1), showing that inhibition of FOXO-1, by pharmacological means or via siRNA, restored insulin-stimulated eNOS phosphorylation. The molecular mechanism for how specific adipose tissue depots alter insulin responses and eNOS activity is still unknown. In another study on a mouse model of obesity and elevated glucose levels, Xia et al demonstrated that the interaction between adipose tissue and endothelial cells is critical in modulating how endothelial cells respond to acetylcholine-induced vasodilation.<sup>14</sup> These authors demonstrated that the perivascular adipose tissue surrounding the aorta from obese mice blunted acetylcholine-dependent vasodilation, and that when the perivascular adipose tissue was removed, the aortas from obese mice had a normal vasodilatory response to acetylcholine, mimicking that of lean mice. The negative effect on vasodilation was mediated by uncoupling of eNOS through reduced availability of L-arginine in perivascular tissue from obese mice. The studies discussed earlier, and others using isolated endothelial cells,<sup>15</sup> highlight the importance of studying cells in their biological context.

However, there seem to be a multitude of mechanisms whereby diabetes mellitus can blunt vasodilation induced by acetylcholine and eNOS. Thus, Hu et al demonstrated that the growth factor platelet-derived growth factor AA (PDGF-AA) impairs acetylcholine-dependent vasodilation in aortas from diabetic db/db mice. Using shRNA and adenoviral-mediated add-back experiments in vivo, the authors demonstrated that bone morphogenic protein 4 induces PDGF-AA, resulting in impaired endothelial function.<sup>16</sup> These authors also

demonstrated that plasma levels of PDGF-AA are increased in both humans and mice with diabetes mellitus, adding PDGF-AA to the family of potential mediators of impaired endothelial function associated with diabetes mellitus.

Other groups have addressed the question of how to repair damaged endothelial cell sites in the presence of diabetes mellitus. Chan et al<sup>17</sup> were recently able to generate early vascular cells with high portions of vascular endothelial cadherin-positive cells from inducible pluripotent stem cells from patients with type 1 diabetes mellitus. These cells formed 3-dimensional vascular networks in vitro and incorporated into the vasculature in a zebra fish model. These studies suggest that a patient's own stem cells could potentially be used in situations in which endothelial cell repair is needed, for example, to increase vascularization during wound healing. It is possible that these inducible pluripotent cells might be less affected by diabetes mellitus than the more differentiated endothelial progenitor cells, which have been shown to be negatively affected by diabetes mellitus.<sup>18</sup>

### **New Mechanistic Insight Into Regulation of Inflammation Associated With Diabetes Mellitus**

Both increased systemic inflammation and increased inflammatory activation of vascular and lesional cells have been postulated to augment the atherosclerotic process in the presence of diabetes mellitus. One of the signaling pathways suggested to be activated in the setting of diabetes mellitus is the janus kinase/signal transducers and activators of transcription pathway. This pathway is normally activated by interferons, interleukins, and growth factors. In an article published recently in *ATVB*, Recio et al demonstrated that systemic administration of a cell-permeable suppressor of cytokine signaling-1 peptide, containing the kinase inhibitory region, reduced measures of inflammation and atherosclerosis in diabetic apolipoprotein E-deficient mice,<sup>19</sup> clearly suggesting that blocking janus kinase/signal transducers and activators of transcription-mediated inflammation impairs lesion formation. The investigators did not test whether this inhibitory effect on atherosclerosis was specific to the diabetic setting. In another study, addressing the role of reactive oxygen species in inflammation and atherosclerosis in diabetic mice, Gray et al found that deficiency in the hydrogen peroxide-generating NADPH oxidase isoform 4 resulted in augmented proinflammatory status, measured as circulating levels of CCL2 (chemokine [CC-motif] ligand 2) and vascular gene expression of several cytokines, and concomitantly accelerated atherosclerosis in apolipoprotein E-deficient diabetic mice.<sup>20</sup> Interestingly, the effect of NADPH oxidase isoform 4 deficiency was only evident in diabetic mice. Reactive oxygen species have been considered protagonists of atherogenesis associated with diabetes mellitus, thus making this data rather surprising. The authors then showed that the superoxide-producing NADPH oxidase isoform 1 clearly has proatherosclerotic properties, suggesting that reactive oxygen species can have divergent effects on inflammation and atherosclerosis, depending on the enzyme generating them.<sup>21</sup>

How is low-grade systemic inflammation induced in subjects with diabetes mellitus? One possibility is that increased

visceral adipose tissue could be a factor setting the stage for a proinflammatory environment. A study of T cells in subcutaneous adipose tissue compared with visceral adipose tissue in nondiabetic obese humans demonstrated a clear increase in proinflammatory Th1 and Th17 CD4 T cells in visceral fat compared with subcutaneous fat, and a correlation between these T cells and systemic inflammation, measured as high-sensitive C-reactive protein.<sup>22</sup> Interestingly, plasma high-sensitive C-reactive protein levels as well as insulin resistance correlated inversely with the level of Th2 levels, potentially suggesting that visceral adiposity results in a defect in anti-inflammatory capacity and insulin resistance. In this context, it is interesting to note that mouse models have suggested that suppression of T cell activation can be used as a treatment strategy to reduce atherosclerosis.<sup>23</sup> In another study, Harmon et al suggested a protective role for IgM-producing B-1b B cells in visceral adipose tissue in insulin-resistant mice.<sup>24</sup> A similar subset of B-1b B cells could also be detected in omental adipose tissue in humans.<sup>24</sup>

The role for local inflammation as the mediator of unstable atherosclerotic lesions in human subjects with type 2 diabetes mellitus was recently investigated. Edsfield et al analyzed carotid endarterectomy specimens and found no increase in inflammatory markers in these advanced lesions from type 2 diabetic subjects, as compared with nondiabetic controls.<sup>25</sup> However, diabetes mellitus was associated with an increased frequency of symptomatic plaques, and these plaques exhibited an association with increased inflammatory gene expression. The authors pointed toward reduced stabilizing fibrous matrix as a potential reason for increased risk of rupture of the atherosclerotic lesions seen in diabetes mellitus. The same group then continued to show that plasma levels of the matrix metalloproteinases 7 and 12 were elevated in type 2 diabetics and were associated with increased incidence of atherosclerosis and cardiovascular disease.<sup>26</sup>

In addition to inflammation, or maybe in conjunction with inflammation, ectopic fat accumulation in the liver is emerging as a risk factor for both diabetes mellitus and cardiovascular disease, topics that are discussed in recent reviews.<sup>27,28</sup> Thus, systemic factors and alterations in adipose tissue and liver might all contribute to a proinflammatory environment likely to promote at least some aspects of diabetic vascular complications, especially in type 2 diabetes mellitus.

### **Abnormal Lipoprotein Metabolism and Function in Macrovascular Disease Risk Associated With Diabetes Mellitus**

In addition to the mechanisms discussed earlier, alterations in lipid metabolism are at the core of diabetes mellitus phenotypes and probably greatly contribute to the increased risk of cardiovascular disease associated with diabetes mellitus. It is well known that suboptimally controlled diabetes mellitus results in elevated triglyceride levels.<sup>29</sup> In this context, Willecke et al recently demonstrated that diabetes mellitus-induced hypertriglyceridemia is driven by insulin deficiency rather than by hyperglycemia in mice and further that hypertriglyceridemia does not develop because of hepatic overproduction of lipids but rather because of a defect in lipolysis



and clearance of triglyceride-rich lipoproteins.<sup>30</sup> One way the liver is responding to insulin deficiency, and one of the ways it can induce dyslipidemia is by upregulating Proprotein Convertase Subtilisin/Kexin Type 9, resulting in degradation of the low-density lipoprotein receptor.<sup>31</sup> Another mechanism whereby insulin deficiency promotes elevated triglycerides is through increased apolipoprotein C-III levels.<sup>32</sup> Apolipoprotein C-III is primarily produced in the liver and intestine. Recently, Qamar et al showed in a cross-sectional study that plasma apolipoprotein C-III levels positively correlate with a proatherogenic lipid profile (increased triglycerides, increased low-density lipoprotein cholesterol, and total cholesterol) and with coronary artery calcification in type 2 diabetics, suggesting that apolipoprotein C-III-induced dyslipidemia might be associated with atherosclerosis in subjects with diabetes mellitus.<sup>33</sup>

HDL cholesterol and more recently HDL function assessed by its ability to accept cholesterol from lipid-laden cells in vitro have been shown to associate with cardiovascular disease protection.<sup>34–36</sup> Conversely, reduced HDL cholesterol levels are associated with increased risk cardiovascular disease. In addition to HDL's direct function in lipid metabolism and transport, HDL cholesterol has been suggested to play a role in glycemic control.<sup>37</sup> Cochran et al recently demonstrated that apolipoprotein A-I, the main structural protein of HDL, increases insulin secretion from Ins-1E  $\beta$ -cells and primary islets through a FOXO1-dependent pathway.<sup>38</sup> Recent studies have suggested that HDL can become dysfunctional in states characterized by increased systemic or vascular inflammation.<sup>39</sup> Data are also now emerging showing dysfunctional HDL in the setting of diabetes mellitus. For example, HDL isolated from interstitial fluid of subjects with type 2 diabetes mellitus was demonstrated to exhibit an impaired capacity to efflux cholesterol from lipid-loaded macrophages.<sup>40</sup> In another study, HDL from subjects with type 2 diabetes was impaired in its ability to protect against oxidative stress in cardiomyocytes through a mechanism that involves depletion of HDL-associated sphingosine-1-phosphate.<sup>41</sup> Interestingly, increased sphingolipids have recently been shown to be associated with symptomatic atherosclerotic plaques and inflammation in humans,<sup>42</sup> raising the possibility of interactions among HDL, sphingolipids, and symptomatic lesions.

### Summary

Recent articles published in *ATVB* have highlighted novel pathways likely to contribute to dysfunction of vascular cells and vascular complications in diabetes mellitus. Several of these studies analyzed endothelial cells freshly isolated from human subjects with diabetes mellitus and controls. Novel approaches to isolation of endothelial cells from subjects with diabetes mellitus are likely to significantly advance our understanding on how diabetes mellitus mediates endothelial cell dysfunction in patients affected by vascular complications. Other studies highlighted the need to study cells in their contextual location in tissues and the role of adipose tissue and other tissues in mediating changes in endothelial cells. New data are emerging on changes in lipoprotein metabolism and function as potentially highly relevant areas of research for

prevention and treatment of vascular complications of diabetes mellitus. These studies open new research areas that will lead to research discoveries likely to impact microvascular and macrovascular complications associated with diabetes mellitus and will bring us closer to successful prevention and treatment strategies for vascular complications of diabetes mellitus.

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### Disclosures

None.

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