

## Highlighting Diabetes Mellitus The Epidemic Continues

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The defining feature of diabetes mellitus is the presence of hyperglycemia.<sup>1</sup> The most common forms of diabetes mellitus are type 1 diabetes mellitus, in which an absolute deficiency of insulin ensues consequent to pancreatic beta cell destruction, and type 2 diabetes mellitus, in which insulin resistance may lead to hyperglycemia.<sup>1</sup> Obesity is an important risk factor for type 2 diabetes mellitus, and it is on the rise.<sup>2</sup> Beyond obesity as a risk factor, it is known that a form of lean diabetes mellitus reflects a phenomenon in which fundamental defects in insulin secretion, on account of pancreatic beta cell dysfunction, primarily trigger the development of diabetes mellitus.<sup>3</sup> As of 2014, 9.3% of Americans were said to have diabetes mellitus (29.1 million people); the lifetime risk for the development of diabetes mellitus in the United States stands at 40%.<sup>2</sup> In addition to those with diagnosed diabetes mellitus, it is estimated that 86.1 million adults in the United States have prediabetes.<sup>2</sup> The complications of diabetes mellitus affect nearly every tissue of the body, and diabetes mellitus is a leading cause of cardiovascular morbidity and mortality, blindness, renal failure, and amputations. Further, the early diagnosis of type 2 diabetes mellitus in adolescents and young adults (≤age 40 years) has been linked to a more aggressive form of the disease, with premature development of serious complications.<sup>4</sup> Together, these sobering statistics underscore the vital importance of uncovering the root causes of diabetes mellitus and its complications to best design strategies for therapeutic intervention in this disorder.

In this “Highlights” on Diabetes Mellitus, a summary of recent articles published in *Arteriosclerosis, Thrombosis, and Vascular Biology (ATVB)* will be presented. Spanning studies at the cellular/molecular and animal model level, to translational and intervention studies in human subjects, these reports offer new insights into the causes and consequences of diabetes mellitus and shed light on plausible therapeutic targets.

### Studies in Animal Models

#### Hyperglycemia, Diabetes Mellitus, and Endothelial Dysfunction

It has long been appreciated that a pivotal and early target for hyperglycemia and its biochemical consequences is the

endothelium.<sup>5</sup> Because the innate functions of the endothelium are geared to protect from oxidative, inflammatory, and procoagulant assaults, it is not surprising that diabetes mellitus causes direct damage to these cells, thereby setting the stage for long-term complications.<sup>6</sup> In a series of recent articles published in *ATVB*, work has been presented to illustrate how diabetes mellitus causes direct damage to endothelial cells (ECs) and, in other contexts, adversely affects the protective functions of these cells. The process of autophagy may exert protective roles in ECs exposed to high levels of glucose, which likely reflects discrete time- and condition-dependent sources of stress.<sup>7,8</sup> Bharath et al<sup>9</sup> recently demonstrated direct links between EC autophagy and glucose metabolism. They demonstrated that when autophagy was compromised in ECs grown from bovine aorta and exposed to shear stress, the production of ATP was suppressed on account of a decrease in glucose uptake and glycolysis and that this prevented shear stress-induced phosphorylation of endothelial NO synthase at serine residue S1117. In that work, experimental strategies to restore glucose transport, glycolysis, and purinergic signaling rescued ECs exposed to shear stress.<sup>9</sup>

The observation that serum PDGF-AA (platelet-derived growth factor-AA) was elevated in diabetic *db/db* mice, a model of type 2 diabetes mellitus, and human diabetic subjects led Hu et al to test potential mechanisms and consequences of this finding. They demonstrated that BMP4 (bone morphogenetic protein 4), which mediates endothelial dysfunction in cardiometabolic diseases,<sup>10</sup> upregulated PDGF-AA via SMAD1/5 and SMAD4 in ECs.<sup>11</sup> In vivo, administration of a neutralizing antibody to PDGF-AA or tail vein injection of a *Pdgfa*-shRNA adenovirus improved endothelial function in both the aortas and mesenteric resistance arteries of *db/db* mice.<sup>11</sup>

In other studies, Chiu et al<sup>12</sup> examined how endothelial dysfunction in diabetes mellitus is linked to impaired cross talk with cardiomyocytes. These authors showed that when ECs derived from rat aorta were exposed to high levels of glucose, the expression of GPIHBP1 (glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1) was induced, which mediated the shuttling of lipoprotein lipase across these cells, thereby regulating lipoprotein lipase-derived fatty acid effects on cells such as cardiomyocytes. They showed that cardiomyocyte release of VEGF (vascular endothelial growth factor), which induces endothelial GPIHBP1 mRNA and protein, is greatly dampened in diabetic animals.<sup>12</sup> ECs were shown to release heparanase in high glucose conditions, thereby providing a mechanism to augment release of myocyte VEGF. The studies of Chiu et al, therefore, demonstrate how EC-cardiomyocyte cross talk is adversely affected by the negative consequences of high glucose.

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Prompted by the observation that atherosclerotic plaques from human diabetic subjects displayed lower amounts of NADPH (nicotinamide adenine dinucleotide phosphate) oxidase 4 (NOX4), Gray et al sought to test its potential role in atherosclerosis. Using *ApoE* (apolipoprotein E)-null mice bred into the NOX4 background and rendered diabetic with streptozotocin, a pancreatic beta cell toxin that induces hyperglycemia, these authors found the surprising result that loss of NOX4 actually increased atherosclerosis, thereby providing evidence that not all sources of reactive oxygen species are detrimental in diabetes mellitus; rather, they may be associated with improved plaque-remodeling potential.<sup>13</sup>

### Insulin, Glycation, Diabetes Mellitus, and Lipid Metabolism

Disorders of lipid metabolism have been extensively studied in both types 1 and 2 diabetes mellitus because such disorders may amplify the risk for cardiovascular disease observed in subjects with diabetes mellitus. Many recent studies in *ATVB* have addressed this important concept. The role of insulin in regulation of PCSK9 (proprotein convertase subtilisin/kexin type 9) was studied by Miao et al.<sup>14</sup> In rat hepatoma cells and primary rat hepatocytes, these authors showed that insulin increased PCSK9 expression and increased degradation of the LDLR (low-density lipoprotein receptor). In mice bearing liver-specific deletion of the insulin receptor, hepatic levels of *Pcsk9* mRNA and plasma levels of PCSK9 were reduced by 55% to 75% and by 75% to 88% in mice rendered insulin deficient by treatment with streptozotocin. Further, they demonstrated that in *ob/ob* mice, deficient in leptin and a model of type 2 diabetes mellitus, treatment with an antisense oligonucleotide to knockdown the insulin receptor reduced PCSK9 levels by 65%. In contrast, this treatment had little effect on PCSK9 levels in lean, nondiabetic mice. They further demonstrated that under the distinct condition of fasting, PCSK9 expression was reduced by 80%, even in mice that lacked hepatic insulin signaling.<sup>14</sup> Together, their studies demonstrated that even though insulin induces PCSK9 expression, other factors clearly may intervene to regulate its expression in discrete conditions. These findings may have important implications on regulation of PCSK9 in human subjects with diabetes mellitus.

The process of nonenzymatic glycation, that is, formation of advanced glycation end products (AGEs), induces profound effects on multiple cell types and tissues in diabetes mellitus.<sup>15</sup> In a recent report, Brinck et al, using in vitro cardiomyocytes and ex vivo approaches in the isolated perfused heart, studied the consequences of glycation of high-density lipoprotein (HDL). They showed that in diabetes mellitus, glycation reduces the sphingosine-1 phosphate (S1P) content of HDL, leading to increased cardiomyocyte cell death. When S1P was added back to diabetic HDL, thereby restoring its content of S1P, cardioprotective functions were restored.<sup>16</sup>

Willecke et al<sup>17</sup> sought to determine mechanisms of diabetic hypertriglyceridemia. Using multiple animal models, they showed that insulin deficiency causes hypertriglyceridemia through decreases in peripheral lipolysis and not via an increase in hepatic triglyceride production and secretion.<sup>17</sup>

### Diabetes Mellitus, Platelets, and Coagulation

The study of disorders of platelets and thrombosis is essential for understanding the breadth of pathological consequences of diabetes mellitus in cardiovascular diseases.<sup>18,19</sup> Recent reports in *ATVB* have addressed these issues. Fidler et al studied fundamental glucose metabolism in platelets; on activation, platelets increase glucose uptake, glycolysis, and glucose oxidation, and consume stored glycogen. These authors specifically addressed the function of GLUT3, a glucose transporter, on platelet function. They used a platelet-specific deletion of *Slc2a3* (gene encoding GLUT3) and showed that loss of GLUT3 in platelets was protective in a mouse model of collagen/epinephrine-induced pulmonary embolism and in the K/BXN model of autoimmune inflammatory disease. Studies at the cellular level supported the conclusions of the in vivo studies because loss of platelet GLUT3 decreased platelet degranulation, spreading, and clot retraction.<sup>20</sup>

Two distinct studies addressed the effects of thrombosis in diabetic kidney disease. First, Dhanesha et al<sup>21</sup> showed, using diabetic mouse models, that a disintegrin and metalloprotease with thrombospondin type I repeats-13 (ADAMTS13) retards progression of nephropathic changes in the diabetic kidney through inhibition of von Willebrand factor-dependent intrarenal thrombosis. In other studies, Oe et al<sup>22</sup> showed that diabetes mellitus increased renal *F10* (Factor X) mRNA, urinary FXa activity, and FX expression in glomerular macrophages and that an inhibitor of FXa ameliorated diabetic kidney pathology, in parallel with reduced expression of proinflammatory and profibrotic genes.

### Diabetes Mellitus, MicroRNAs, and Chromatin Modification

MicroRNAs (miRNAs) have received considerable attention in the study of mechanisms of diabetes mellitus and its complications.<sup>23</sup> Recent work published in *ATVB* adds to the body of evidence linking miRNAs to diabetes mellitus and its complications. Human umbilical vein ECs were isolated from normal healthy versus gestational diabetes mellitus pregnancies and tested for their functional properties. The human umbilical vein ECs from gestational diabetes mellitus pregnancies displayed reduced function, in parallel with higher miR-101 expression and reduced expression of one of its targets, zester homolog-2 (EZH2), which trimethylates histone 3/lysine 27, thus repressing gene transcription. When miR-101 was inhibited in these cells, endothelial function improved. In vitro, healthy human umbilical vein ECs exposed to high levels of glucose recapitulated the phenotype of gestational diabetes mellitus because miR-101 levels were increased.<sup>24</sup>

In other studies, Li et al<sup>25</sup> showed that hyperglycemia and high levels of free fatty acids in diabetes mellitus recruit p66Shc, resulting in upregulation of miR-34a via an oxidative stress-sensitive mechanism, which targets SIRT1 (sirtuin 1), leading to endothelial dysfunction. Further, Reddy et al<sup>26</sup> showed that miR-504 was upregulated in vascular smooth muscle cells by high glucose and palmitic acid, which was accompanied by upregulation of proinflammatory genes. Finally, in a recent review published in *ATVB*, Schones et al<sup>27</sup> summarized current knowledge of chromatin modifications and their associations with diabetes mellitus and obesity.

## Diabetes Mellitus: Tissue Damage and Healing and Therapeutic Opportunities

The problem of impaired wound healing in diabetes mellitus is a long and persistent one.<sup>28</sup> Recent state-of-the-art advances have highlighted opportunities to use biomaterials to rewire the plagued diabetic wound.<sup>29</sup> Recent reports in *ATVB* have continued to explore mechanisms of impaired wound healing in diabetes mellitus and to highlight novel therapeutic opportunities.

Zhang et al<sup>30</sup> showed that protein tyrosine phosphatase 1B impairs wound healing by dephosphorylating the EC VEGF receptor 2, thereby providing a mechanism to suppress proliferation, migration, and tube formation of ECs. In a model of femoral artery ligation in diabetic mice, López-Díez et al<sup>31</sup> showed that deletion of *Ager* (gene encoding the receptor for AGEs) in diabetic mice restored effective inflammatory responses in the ischemic muscle tissue, in parallel with increased blood flow and angiogenesis, as measured by laser Doppler imaging and CD31<sup>+</sup> cellular content in the injured muscle tissue, respectively, 28 days after ligation.

Chan et al sought to correct the defects in wound and tissue healing associated with diabetes mellitus. They engineered a 3-dimensional vascular network in synthetic hydrogels from type 1 diabetic patient-derived human induced pluripotent stem cells to develop an autologous vascular therapy for diabetes mellitus. These authors showed that early ECs from these type 1 diabetic human induced pluripotent stem cells were functional when mature; their work provides a framework for novel tissue-engineering strategies to combat the maladaptive effects of hyperglycemia on endothelial progenitors and ECs in diabetes mellitus.<sup>32</sup>

Studies in cellular and animal models published in *ATVB* were complemented by a series of articles in which the mechanisms and consequences of diabetes mellitus were explored in human subjects, which will be reviewed in the section to follow.

### Studies in Human Subjects

Recent articles published on the subject of diabetes mellitus and its complications in *ATVB* have also focused on uncovering the epidemiology of these disorders, underlying mechanisms, and new therapeutic targets, with a focus on human subject research.

### Epidemiology and Pathology of Diabetes Mellitus and Vascular Disease

Yahagi et al<sup>33</sup> from the laboratory of Renu Virmani recently reviewed the pathology of the diabetic human coronary and carotid atherosclerosis and vascular calcification. These authors summarized that coronary artery plaques of human subjects with types 1 or 2 diabetes mellitus demonstrated larger necrotic cores and greater degrees of inflammation, as manifested by higher macrophage and T-cell content. Further, these authors reported that lesion calcification in the coronary, carotid, and other arterial beds was more extensive in diabetic versus nondiabetic subjects. This work continues to set the stage for the pursuit of the underlying mechanisms and supports the premise that distinct vascular beds must be examined

uniquely for clues and cues mediating the initiation and progression of disease in diabetes mellitus.

Investigators from the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study) aimed to analyze atherosclerotic cardiovascular disease in different arterial territories in subjects with familial hypercholesterolemia versus their nonaffected relatives and reported that coronary artery and peripheral artery manifestations of disease were more prevalent in familial hypercholesterolemia subjects versus the non-familial hypercholesterolemia controls but that no significant differences were found in cerebrovascular events.<sup>34</sup> In that study, age, body mass index, type 2 diabetes mellitus status, high blood pressure, previous use of tobacco, and lipoprotein(a) levels >50 mg/dL were independently associated with atherosclerotic cardiovascular disease.

In 2 other recent studies in *ATVB*, the authors examined the effect of metabolic factors on vascular disease risk. First, Yamazoe et al queried the relationship between insulin resistance and coronary artery calcification after adjustment for metabolic syndrome to determine whether insulin resistance is associated with the prevalence of calcification or progression and whether it is independent of metabolic syndrome. To accomplish this, they conducted a population-based study in a random sample of Japanese men, aged 40 to 79 years, in which insulin resistance was measured using the homeostasis model assessment of insulin resistance model. In total, 1006 participants entered the study and 789 were followed up for a mean duration of ≈4.9 years. After adjustment for covariates including factors related to the metabolic syndrome, homeostasis model assessment of insulin resistance was determined to be independently associated with coronary artery calcification prevalence and progression.<sup>35</sup>

Second, a striking milieu in which diabetes mellitus seems to be inversely associated with vascular disease pathology is in the setting of abdominal aortic aneurysms (AAA).<sup>36</sup> Interestingly, levels of circulating plasma/serum ligands of receptor for AGEs, known to be increased in atherosclerotic cardiovascular disease, have been reported to be lower in subjects in the Health in Men Study with AAA; levels of a specific AGE, carboxy methyl lysine AGE, were lower in diabetic subjects with AAA versus controls.<sup>37</sup> What about the pre-AGE species, that is, glycosylated hemoglobin (HbA1C)? Kristensen et al<sup>38</sup> examined levels of HbA1C in a screening trial for AAA in men aged 65 to 74 years in the Central Denmark Region. The authors found an inverse association between the growth rate of AAA and the level of HbA1C. The results of these studies, collectively, might spur further basic science experimentation to discern the mechanisms by which diabetes mellitus exerts these protective effects in AAA, as they may uncover putative therapeutic targets for limiting growth of AAAs.

### Diabetes Mellitus and Vascular Function

As in animal subjects, the measures of vascular and specifically endothelial function are typically measured in human subjects to gauge or biomark the status of disease. Hendriks et al<sup>39</sup> studied a high-risk population from the SMART study (Second Manifestations of Arterial Disease) and showed that

an ankle-brachial index  $\geq 2.4$  was associated with increased risk for myocardial infarction but not with stroke, all-cause mortality, or vascular mortality.

Using Doppler flowmetry in response to iontophoresis of acetylcholine and sodium nitroprusside, Walther et al showed that metabolic syndrome was associated with endothelial dependent and endothelial independent dysfunction, which affected both the macro- and the microvascular systems and that subjects with diabetes mellitus had the most smooth muscle cell dysfunction. Finally, they showed that central abdominal fat and systemic inflammation were implicated in the vascular dysfunction of the metabolic syndrome.<sup>40</sup>

From the CODAM study (Cohort on Diabetes and Atherosclerosis Maastricht), Hertle et al<sup>41</sup> examined carotid artery intima-media thickness and the association with markers of endothelial dysfunction, circulating mannose-binding lectins, and their associated proteases 1-2-3 and MAP44 and showed that MASP-3 and Pap44 may play a role in endothelial dysfunction.

The accessibility of human ECs prompted Bretón-Romero et al to measure flow-mediated dilation of the brachial artery from 85 subjects with type 2 diabetes mellitus and age-matched controls to assess potential mediators of endothelial dysfunction. The ECs from diabetic subjects displayed significantly higher Wnt5a and JNK activation levels and the higher JNK activation was associated with lower flow-mediated dilation, an evidence of endothelial dysfunction. In human ECs, Wnt5a and JNK inhibition reversed impairment of endothelial NO synthase activation and NO production.<sup>42</sup>

Smits et al tested the potential benefits of glucagon-like peptide-1 (GLP-1)-based therapies (GLP-1 receptor agonists or dipeptidyl peptidase [DPP] inhibitors) on microvascular function in patients with type 2 diabetes mellitus. They used nail fold skin capillary videomicroscopy and vasomotion by laser Doppler fluxmetry to measure vascular functions and reported that acute treatment with exenatide (GLP-1 receptor agonist) does not affect skin capillary perfusion in diabetes mellitus and that 12-week treatment with either liraglutide (GLP-1 receptor agonist) or sitagliptin (DPP-4 inhibitor) has no effect on capillary perfusion or vasomotion in subjects with type 2 diabetes mellitus.<sup>43</sup> The authors concluded that the effects of these agents on glucose are not mediated through microvascular responses. Importantly, they underscore the key point that the complications of diabetes mellitus are complex and not necessarily readily reversed, thus suggesting contribution from multiple factors beyond the immediate effects of high glucose.

Taken together, these studies reinforce that endothelial dysfunction accompanies metabolic syndrome and diabetes mellitus and highlight the need to identify potential therapeutic avenues to reduce the deleterious effects of metabolic disease on vascular function.

### Diabetes Mellitus, Metabolic Disease, and Perturbation of Lipid Metabolism

As in animal model studies, the links between metabolic diseases such as diabetes mellitus and lipid abnormalities remain a highly studied area of investigation. In recent years, key

articles in this area have been published in *ATVB*, which span the range from epidemiology to therapeutic interventions.

Two recent reports examined levels of common lipid-related species with vascular disease. First, Liu et al tested the association of plasma levels of fatty acid-binding protein 4, retinol-binding protein 4, and high-molecular-weight adiponectin with cardiovascular mortality in men with type 2 diabetes mellitus enrolled in the Health Professionals Follow-up Study after an average of 22-year follow-up. These authors showed that higher levels of fatty acid-binding protein 4 and high-molecular-weight adiponectin were associated with elevated cardiovascular disease mortality in men with type 2 diabetes mellitus.<sup>44</sup> In the second study, Qamar et al<sup>45</sup> performed a cross-sectional study of 1422 subjects with type 2 diabetes mellitus but without evidence of coronary artery disease and found that ApoC-III levels were associated with higher levels of triglycerides and higher coronary artery calcification, together with less favorable cardiometabolic phenotypes. These authors concluded that targeting ApoC-III might reduce cardiovascular risk in type 2 diabetes mellitus.

Adipocyte lipid biology was studied by Rydén and Arner in a recent article in *ATVB* in which they sought to discern the contribution of different lipolysis measures in adipose tissue; this was examined in isolated subcutaneous adipocytes in 1066 men and women. Basal lipolysis and insulin-mediated inhibition of lipolysis were tested. The authors reported that subcutaneous fat cell lipolysis is an independent contributor to interindividual variations in plasma lipids and that high spontaneous lipolysis activity and resistance to the antilipolytic effect of insulin associate with elevated triglyceride and low HDL cholesterol concentrations.<sup>46</sup>

It has been reported that HDL particles in the plasma of subjects with type 2 diabetes mellitus have impaired cholesterol efflux capacity.<sup>47</sup> In a study by Apro et al, the authors queried whether efflux capacity of HDL from the interstitial fluid, a key starting point for reverse cholesterol transport, was also affected in type 2 diabetes mellitus. They found strikingly greater impairment in the efflux capacity to interstitial fluid in the diabetic subjects, compared with the efflux capacity of plasma HDL, thereby suggesting that impairment in cholesterol efflux capacity of HDL from interstitial fluid may contribute to the excess cardiovascular disease observed in diabetes mellitus.<sup>48</sup>

Two distinct studies in *ATVB* examined the nature of HDL particles in human diabetes mellitus. First, Frej et al studied ApoM (apolipoprotein M) and S1P from plasma of 42 controls and 89 type 1 diabetic subjects. They tested the ability of these particles to inhibit inflammation in primary human aortic ECs and reported that ApoM/S1P in light HDL particles were inefficient in inhibition of vascular inflammation in the isolated ECs in contrast to the denser ApoM/S1P particles. Because the type 1 diabetic subjects had a higher proportion of light versus the heavy particles, those findings might identify new contributing mechanisms and biomarkers of cardiovascular disease in type 1 diabetes mellitus.<sup>49</sup> In the second study, the HDL from subjects with metabolic syndrome, but not diabetes mellitus, was examined for its ability to activate endothelial NO synthase. Denimal et al<sup>50</sup> showed that even before the development of diabetes mellitus, subjects with

metabolic syndrome display reduced activation of endothelial NO synthase by their HDL; this was traced to a depletion of SIP in the HDL, thereby highlighting diabetes mellitus-independent mechanisms for increased atherogenic properties of HDL in the metabolic syndrome.

Four recent studies published in *ATVB* examined the effect of various interventions on lipid biology in human subjects. First, Xiao et al studied 9 healthy normolipidemic and normoglycemic men treated with either intranasal insulin (at a dose previously shown to reduce hepatic glucose production) or placebo. They showed that insulin administration by the intranasal route reduces hepatic glucose production but has no effect on triglyceride-rich lipoprotein particle production by the liver and intestine.<sup>51</sup> Second, in a distinct study, Xiao et al<sup>52</sup> administered glucose by systemic intravenous injection to healthy nondiabetic men and showed that short-term glucose infusions stimulate intestinal lipoprotein production. In contrast to the first 2 studies, in which acute, short-term treatments with insulin or glucose were administered to healthy subjects, 2 distinct reports examined longer term treatments with lipid-modulating agents in subjects with type 2 diabetes mellitus.

Ooi et al<sup>53</sup> tested the effects of extended niacin on the metabolism of Lp(a)- and apoB-100-containing lipoproteins in 11 statin-treated men with type 2 diabetes mellitus and reported that extended niacin decreased plasma Lp(a) concentrations by decreasing the production of Apo-a and Lp(a)-apoB-100. The second study was prompted by the increasing evidence that perturbed lipid metabolism is a key contributor to the pathogenesis of diabetic kidney disease.<sup>54</sup> Jin et al administered probucol versus placebo to type 2 diabetic subjects with albuminuria already using renin-angiotensin blockade during a 16-week randomized, double-blind, placebo-controlled trial. These authors reported that although probucol treatment resulted in significantly lowered total cholesterol and low-density lipoprotein cholesterol levels, no reduction in urinary albumin excretion was observed. However, it is to be noted that the majority of the subjects were already on statin therapy.<sup>55</sup>

Taken together, these studies on the links between lipoprotein metabolism, metabolic syndrome, and diabetes mellitus (types 1 and 2)—from observational to interventional—underscore that much more needs to be learned on lipid perturbation in the vascular and nonvascular complications of diabetes mellitus and how to optimally leverage scientific advances in lipid biology in the therapeutic armamentarium.

### Diabetes Mellitus and Inflammation

Certainly, multiple studies have solidified a link between inflammation and both the development of diabetes mellitus and the exacerbation of cardiovascular disease in subjects with established diabetes mellitus. Recent studies published in *ATVB* in human subjects affirm this critical relationship and offer possible avenues for therapeutic intervention. Goncalves et al<sup>56</sup> showed that levels of matrix metalloproteinases 7 and 12 are elevated in subjects with type 2 diabetes mellitus and are associated with more severe atherosclerosis and increased incidence of coronary events. Akinkuolie et al studied 26 508

initially healthy women free from diabetes mellitus and reported that a consensus glycan sequence common to many acute-phase reactants was linked to the risk of development of type 2 diabetes mellitus, thereby affirming the association between inflammation and the risk of diabetes mellitus itself.<sup>57</sup> Pedersen et al examined associations of plasma kynurenines with risk of acute myocardial infarction in patients with stable angina pectoris; the choice of marker was based on the fact that enhanced tryptophan degradation is induced by the cytokine, interferon- $\gamma$ . The authors showed that elevated levels of plasma kynurenines predicted risk of acute myocardial infarction, with the risk estimates being generally stronger in subjects with abnormalities of glucose homeostasis.<sup>58</sup>

Finally, Durda et al examined plasma levels of soluble interleukin-2 receptor alpha in 4408 European Americans and 766 African Americans from the Cardiovascular Health Study and found that after adjustment for baseline cardiovascular disease risk factors, levels of sIL-2R $\alpha$  in both ethnic groups were associated with all-cause mortality, cardiovascular disease mortality, and heart failure. Of note, when adjusted for age, sex, and race, sIL-2 $\alpha$  was positively associated with type 2 diabetes mellitus as well.<sup>59</sup> Taken together, these studies add further affirmation to the proposed models in which inflammation increases both the risk of diabetes mellitus and the development of cardiovascular complications.

### Diabetes Mellitus and MiRNAs

Akin to studies in animal models, there is considerable interest in the roles of microRNAs in diabetes mellitus and vascular complications. Recent studies published in *ATVB* have used human subject materials to address these questions. One of these recent studies focused on miR-126, a miRNA previously linked to diabetes mellitus and its complications, both mechanistically and as a potential biomarker.<sup>60-62</sup> Witkowski et al examined plasma samples from subjects with diabetes mellitus for tissue factor protein and activity, together with miR-126 expression pre- and post-optimization of diabetes mellitus treatments. These authors found that low levels of miR-126 were associated with striking increases in levels of tissue factor protein and activity, which was accompanied by evidence of increased inflammation and higher leukocyte counts.<sup>63</sup> As diabetic treatment was administered, the levels of miR-126 rose, and thrombogenicity was reduced. Molecular studies traced the mechanism to miR-126 binding to the 3'-untranslated region of the tissue factor gene, *F3*. These seminal findings link miR-126 to control of hemostatic balance in the vasculature, which is perturbed in diabetes mellitus. In a second study, Dangwal et al performed miRNA profiling and confirmed alterations in circulating levels of miR-191 and miR-200b in diabetic versus control subjects. In dermal cells, these authors showed that these cells took up endothelial derived miR-191, leading to downregulation of a key target, zonula occludens-1. Through zonula occludens-1, altered miR-191 expression influenced angiogenesis and migratory capacity of diabetic dermal ECs or fibroblasts, respectively.<sup>64</sup> Those results directly linked an altered expression of a miRNA in diabetes mellitus to delays in tissue repair processes.<sup>64,65</sup>

## Summary

In summary, recent reports published in *ATVB* have used a broad range of innovative cellular to animal model to human subject materials to broaden our understanding of the mechanisms linked to the pathogenesis of diabetes mellitus and its complications. Because the epidemic of diabetes mellitus continues unabated, to date, these reports serve to stimulate identification of new mechanisms and therapeutic avenues and opportunities. Here, at *ATVB*, we are committed to furthering the breadth of knowledge in the study of diabetes mellitus, its causes, and its cardiovascular and microvascular sequelae.

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## Disclosures

None.

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KEY WORDS: diabetes mellitus ■ glucose ■ human ■ hyperglycemia ■ models, animal



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