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Is Diabetic Macrovascular Disease a Complication of Microvascular Disease?

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Editorial

A causative role for hyperglycemia in the development of diabetic microvascular complications is very clear. In fact, the glycemic parameters that are used to define/diagnose diabetes mellitus (fasting blood glucose >7 mM) were chosen because they effectively differentiate individuals at high risk for developing retinopathy from those at low risk [1]. In contrast, the association between hyperglycemia and macrovascular disease appears to be much more complex. There is a progressive relationship between increasing blood glucose concentration and Cardiovascular Disease (CVD), with CV risk rising approximately 20% for every 1.5 mM increase in fasting glucose, or for every 1% elevation in HbA_{1c} levels [2,3]. Furthermore, both epidemiological and pathophysiological studies have shown that hyperglycemia is an independent CV risk factor. Unexpectedly, clinical trials, including ACCORD, ADVANCE and VADT, have shown that intensive glucose lowering does not prevent macrovascular complications in older patients with long-standing diabetes and existing CV risk factors [4]. In contrast, other trials in younger patients, have shown that glucose lowering is associated with reduced carotid atherosclerosis and CVD in patients with T1D, and has a significant cardiovascular benefit in patients with T2D [5-7].

Traditionally the micro- and macrovascular complications of diabetes have been viewed, and treated, as distinct and independent conditions. However, there is a strong association between the incidence of diabetic micro- and macrovascular disease. A recent meta-analysis of 21 epidemiologic studies of people with either type 1 or type 2 diabetes reported a 2-4 fold higher risk of future ischemic cardiovascular events in those with retinopathy versus those without retinopathy [8]. Moreover, the risk of cardiovascular events rises with the degree of retinopathy.

The mechanisms by which hyperglycemia disrupts normal microvascular structure/function have not been clearly defined but may involve oxidative stress/Advanced Glycation End products (AGEs) and/or Endoplasmic Reticulum (ER) stress. Inflammation, pericyte loss, increased extracellular matrix deposition, and ultimately, increased vascular permeability and vessel leakage are characteristics of micro vessel disease. Depending upon the tissue/organ being considered and the duration of disease, the effects of hyperglycemia on the microvasculature can lead to excessive neovascularization, as in proliferative diabetic retinopathy and nephropathy, or attenuated neovascularization, contributing to pre-proliferative retinopathy, impaired coronary collateral vessel development, impaired wound healing, and transplant rejection in diabetic recipients. The concurrent existence of pro- and anti-neovascularization responses in diabetes has been called the "angiogenesis paradox" [9].

Angiogenesis is the formation of new blood vessels from pre-existing vessels [10]. Inflammation and oxidative stress modulate angiogenesis by regulating the expression/stability of the Hypoxia-Inducible Factor (HIF)-1α [11]. Hypoxia stimulates angiogenesis by inhibiting degradation of HIF-1α, thereby increasing its activity.HIF-1α is a transcription factor that acts, in concert with HIF-1β and p300, to up regulate the expression of many pro- angiogenic cytokines and growth factors, including Vascular Endothelial Growth Factor (VEGF). VEGF is secreted by hypoxic cells and interacts with receptors (VEGFR1/2) found on endothelial cells (and other cell types). This initiates angiogenic processes that ultimately result in increased blood flow and reoxygenation of hypoxic tissues. The mechanisms by which diabetes/hyperglycemia may affect angiogenesis are not well understood. The angiogenesis paradox is most strikingly illustrated by the fact that experimental treatments for proliferative diabetic retinopathy and nephropathy involve targeting VEGF for inhibition, whereas application of exogenous VEGF facilitates wound healing in diabetic patients [12,13].

The vasa vasorum consists of anetwork of small arterioles, capillaries and venules that supply

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the cells that constitute the adventitia and tunica media of large blood vessels, including the aorta and coronary arteries [14]. Vasa vasorum literally means "vessels of the vessels", and therefore, by definition, it is the place where the microvasculature and the macrovasculature directly interact. A role for the vasa vasorum in the progression of atherosclerosis is not a new idea, but historically, it has been a contentious one. A correlation between advential neovascularization and atherosclerotic lesion size has been observed in (non-diabetic) humans and in atherogenic mouse models [15,16]. The cause-effect relationship between lesion neovascularization and atherogenesis in these models is not clear - Does lesion growth promote vasa vasorum angiogenesis, or does vasa vasorum expansion drive lesion growth? Furthermore, what are the macrovascular consequences of impaired vasa vasorum neovascularization?

Because the fundamental purpose of the vasa vasorum is to facilitate the supply, maintenance and repair of the healthy arterial wall, disruption of this microvascular network is likely detrimental. Occlusion of the vasa vasorum has been associated with localized ischemia in the arterial media that may lead to the proliferation of smooth muscle cells, localized intimal/medial thickening, and increased synthesis of collagen fibers [17-19]. Other studies have suggested that the vasa vasorum plays an important role in reverse cholesterol transport and removal of lipids from the artery wall [20]. Relatively early in atherogenesis, the increased oxygen demands associated with inflammation together with subintimal thickening of the artery wall create localized regions of hypoxia. Hypoxia can directly contribute to atherogenesis by promoting foam cell formation through the induction of fatty acid biosynthesis and inhibition of fatty acid oxidation and cholesterol efflux [21]. Hypoxia and elevated levels of HIF-1α have been implicated in promoting inflammatory M1 macrophage polarization and potentiating IL-1β production [22]. Hypoxic cells shift their metabolism to anaerobic glycolysis resulting in the production of reactive oxygen species and reduced ATP availability that may lead to cell death, thereby contributing to growth of the necrotic core [23].

Conversely, other studies have shown that systemic application of pro-angiogenic stimuli is associated with enhanced atherosclerosis, and anti-angiogenic therapies attenuate atherosclerosis [24-26]. It is possible that abnormally enhanced, or attenuated, neovascularization of the vasa vasorum can be detrimental to artery health. It is also important to note that all prior studies have been performed in non-diabetic/normoglycemic animal models. The effects of diabetes/hyperglycemia on vasa vasorum structure and function had not been investigated - prior to our recent study [26].

Our findings have shown that atherosclerotic lesion growth in normoglycemic ApoE$^{-/-}$ mice is associated with expansion in the number of micro vessels of the vasa vasorum [26]. This likely corresponds to the increasing blood supply demands of the thickening artery wall and is consistent with previous reports [15]. In contrast, in hyperglycemic ApoE$^{-/-}$ mice, we observed significantly impaired expansion of the vasa vasorum in atherosclerotic regions compared with atherosclerosis-free regions. This is despite the fact that the lesion volumes in hyperglycemic mice are at least 2× larger than those in normoglycemic mice at 15 weeks of age. Insulin supplementation of STZ-injected ApoE$^{-/-}$ mice normalizes blood glucose levels, rescues vasa vasorum deficiency, and attenuates atherosclerosis. Similar results were obtained in hyperglycemic ApoE$^{-/-}$/Ins2$^{+/Akita}$ mice. Taken together these data are the first evidence that: i) hyperglycemia attenuates neovascularization of the vasa vasorum during normal artery development and especially during atherogenesis and, ii) expansion of the vasa vasorum is not required to support (or promote) accelerated atherosclerosis in these models. We found that hyperglycemic mice have significantly elevated levels of lesional hypoxia and HIF-1, but significantly less lesional VEGF, relative to normoglycemic controls. These findings suggest that there is a "disconnect" between pro-angiogenic stimuli (hypoxia, HIF1α) and response (VEGF, angiogenesis) leading to increased hypoxia and accelerated atherosclerosis.

In summary we propose that that the disruptive affects of hyperglycemia on the microvasculature of the vasa vasorum contributes to the accelerated development of atherosclerosis in diabetes. This could mean that macrovascular disease is, in fact, another microvascular complication of diabetes.

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