Is Type 2 Diabetes Mellitus a Vascular Condition?

Frank B. Hu, Meir J. Stampfer

Cardiovascular disease (CVD) is the most common complication of type 2 diabetes. However, CVD risk factors are elevated long before the development of diabetes, and the development of CVD can also precede the clinical diagnosis of type 2 diabetes. The close relationship between diabetes and CVD has led to the “common-soil” hypothesis, postulating that type 2 diabetes and CVD share common genetic and environmental antecedents, ie, “they spring from a common soil.” The hypothesis implies that atherosclerosis might not be simply a consequence of diabetes but that diabetes and CVD are a single entity sharing an underlying pathophysiology.

See page 1845

Multiple lines of evidence support the common-soil hypothesis. In epidemiologic studies, the same set of diet and lifestyle factors (a diet higher in glycemic load and trans fat and lower in fiber and polyunsaturated fat, smoking, overweight and obesity, lack of regular exercise, and abstinence from alcohol) explains more than 80% of cases of coronary heart disease and 90% of cases of type 2 diabetes. Low birth weight, a marker of intrauterine nutritional deficiency, has been associated with increased risk of both diabetes and CVD in later life. In addition, pharmacological and lifestyle strategies to prevent type 2 diabetes have resulted in significant reductions in the occurrence of the metabolic syndrome and cardiovascular risk factors in subjects with impaired glucose tolerance, although it remains to be seen whether this will translate into a reduction in clinical CVD events. Furthermore, hypertension and dyslipidemia are significant predictors of type 2 diabetes, and statins and angiotensin-converting enzyme (ACE) inhibitors, which are effective in CHD prevention, have been associated with a reduced risk of incident type 2 diabetes in secondary analyses.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Hunt et al provide further direct evidence for the link between diabetes and atherosclerosis. Their careful study found that, after adjustment for age and sex, both common and internal carotid artery intima-media thickness (IMT) were significantly higher among 66 prediabetic individuals than among 1 127 nondiabetic individuals who remained free of diabetes. Also, elevated IMT was a significant predictor of incident type 2 diabetes during follow-up in age- and sex-adjusted analyses. These associations became nonsignificant after further adjustment for elements of the metabolic syndrome, such as blood lipids, blood pressure, 2-hour glucose, and central obesity, suggesting that the metabolic syndrome constitutes the common antecedent linking diabetes and progression of atherosclerosis. This important study provides the first evidence that subclinical atherosclerosis predicts future risk of type 2 diabetes.

At the cellular level, the mechanisms linking metabolic syndrome, type 2 diabetes, and atherosclerosis have not been clearly defined. However, emerging data suggest that diabetes and CVD are both vascular conditions that share an underlying pathophysiology, ie, endothelial dysfunction. The theory postulates that, whereas clinical CVD is a result of endothelial dysfunction in large- and medium-sized arteries, type 2 diabetes is induced by dysfunction in the capillary and arteriolar endothelium, with a vast surface area in intimate contact with metabolically active, insulin-sensitive tissues such as skeletal muscle. It is thought that chronic endothelial activation and impaired nitric oxide–mediated vasodilatation directly cause inadequate insulin delivery to these tissues, resulting in peripheral insulin resistance and reduced glucose uptake.

Historically, the vascular endothelium was thought to be a static monolayer of cells in the body, acting as a semipermeable barrier between the bloodstream and tissue. It is now understood that the endothelium is an active and dynamic tissue essential to maintaining homeostasis of cell adhesion and migration, thrombosis, and fibrinolysis. When the vascular endothelium encounters pro-inflammatory stimuli, endothelial cells are activated by increasing production and expression of soluble adhesion molecules such as ICAM-1, VCAM-1, and E- and P-selectin. Plasma levels of these molecules are significantly elevated in both type 1 and type 2 diabetic patients compared with matched controls, and elevated levels appear to be strongly related to plasma lipids, metabolic control, and markers of oxidative stress. Patients with elevated triglycerides and low HDL had significantly increased levels of ICAM-1, VCAM-1, and E-selectin. Two prospective studies have shown that elevated levels of ICAM-1 and E-selectin significantly predict future risk of CVD. Recently, elevated E-selectin was found to be a strong independent predictor of type 2 diabetes in the Nurses’ Health Study. In addition, Meigs et al found that microalbuminuria, a marker of diffuse endothelial dysfunction, was associated with type 2 diabetes and with CVD. These results support the idea that endothelial dysfunction is a common precursor of both diabetes and CVD.

Another line of evidence supporting the vascular etiology of type 2 diabetes comes from recent evidence that chronic inflammation may be involved in the pathogenesis of insulin resistance and type 2 diabetes. The concept of atherosclerosis as an inflammatory disease is now well established. Recent data have demonstrated that elevated levels of C-reactive protein (CRP), a sensitive marker of chronic inflammation, are associated with obesity, insulin resistance, and glucose intolerance. In several prospective studies, elevated CRP levels
significantly predict risk of type 2 diabetes.\textsuperscript{26–29} In addition, pro-inflammatory adipocyte cytokines, such as tumor necrosis factor alpha-\(\alpha\) (TNF-\(\alpha\)) and IL-6, are significantly elevated in type 2 diabetes.\textsuperscript{29} Elevated production of TNF-\(\alpha\) and IL-6 elicit the production of acute phase reactants such as CRP and fibrinogen by the liver. TNF-\(\alpha\), IL-6, and CRP in turn stimulate endothelial production of adhesion molecules such as ICAM, VCAM, and E-selectin. These pro-inflammatory cytokines and molecules directly affect vascular walls, not only promoting atherosclerosis, but also leading to impaired vascular reactivity, reduced insulin delivery, and increased peripheral insulin resistance.\textsuperscript{30} Thus, vascular endothelial dysfunction can be considered a unifying factor for the diabetogenic effects of excess adiposity, low-grade inflammation, and the metabolic syndrome, as well as the common soil for diabetes and CVD.

The concept of diabetes as a vascular condition not only gives rise to a new paradigm for understanding the etiology of diabetes and CVD, but it also has implications for the prevention and treatment of the two conditions. First, elevated levels of inflammatory and endothelial markers may help identify populations at high risk for both type 2 diabetes and CVD. So far, CRP appears to be the most consistent and robust predictor of both conditions. Second, if endothelial dysfunction is the root cause of both diabetes and CVD, strategies to improve endothelial dysfunction and reduce chronic inflammation should be able to help prevent and treat both conditions. Therapies with statins and ACE inhibitors, which have been shown to reduce CRP and endothelial markers, have also been associated with a reduced risk of incident type 2 diabetes.\textsuperscript{8–10} On the other hand, insulin-sensitizing agents such as metformin and thiazolidinediones, which also improve endothelial function, may prove to play a role in the prevention of both diabetes and CVD. Nonetheless, modification of diet and lifestyle factors, which are fundamental causes of type 2 diabetes and CVD, should remain the first line of defense against heightened chronic inflammation and generalized endothelial dysfunction.

References


Is Type 2 Diabetes Mellitus a Vascular Condition?
Frank B. Hu and Meir J. Stampfer

Arterioscler Thromb Vasc Biol. 2003;23:1715-1716
doi: 10.1161/01.ATV.0000094360.38911.71
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/23/10/1715

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/