Unraveling the Links Between Diabetes, Obesity, and Cardiovascular Disease

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Patients with diabetes mellitus are known to be at increased risk for coronary artery disease and myocardial infarction, and have worse outcomes after coronary interventions such as stenting. The mechanisms for this increased risk are not fully known, but are thought to reflect vascular abnormalities of inflammation, hypertension, dyslipidemia, and hypercoagulability. In turn, these vascular abnormalities may be the result of hyperglycemia, insulin resistance, and advanced glycation products seen in diabetes. However, the precise molecular links between the metabolic abnormalities seen in diabetes, and the resulting vascular changes that increase propensity for atherosclerosis are not clearly understood.

One such link is endothelial dysfunction, seen in diabetes, obesity, hypertension, hyperlipidemia, smoking, and aging. Endothelial dysfunction is characterized by defects in the normal vascular relaxation response to mediators such as acetylcholine, or to increased blood flow. This can be clinically measured by ultrasound studies of forearm blood flow responses. The basis for endothelial dysfunction may involve a reduction in the amount of bioavailable nitric oxide (NO) in the vasculature. NO is necessary for vascular relaxation and endothelium dependent relaxing factor (EDRF) activity. NO also serves to suppress atherosclerosis by reducing endothelial cell activation, smooth muscle proliferation, leukocyte activation and leukocyte-endothelial interactions, and platelet aggregation and adhesion. Therefore, reduction in the amount of bioavailable NO would result in a proatherogenic state.

In this issue, Molnar et al describe a mouse model of type 2 diabetes in which they fed C57BL/6 wild-type mice a high-fat diet and sucrose for 9 weeks. These mice developed changes consistent with diabetes, including obesity, hyperglycemia, and hyperinsulinemia. The authors found that these mice show marked attenuation of endothelium-dependent vasodilation to acetylcholine. They also demonstrated minor alterations in response to the endothelium-independent vasodilator sodium nitroprusside and in the vasoconstrictor response to phenylephrine. These results confirm that the primary metabolic changes caused by the high-fat and sucrose diet are sufficient to cause abnormalities in vascular function. But what are the mechanisms for these abnormalities?

Several pathways may lead to endothelial dysfunction, as outlined in the Figure. First, eNOS mRNA or protein expression levels may be diminished. Second, tissue levels of L-arginine, the substrate for NO production, may be limited. An endogenous competitive inhibitor, asymmetric dimethyl-arginine (ADMA) can reduce endothelial NO production even in the presence of adequate L-arginine levels. Third, cofactors of eNOS may be limiting: eNOS requires FAD, FMN, NADPH, and BH4 as cofactors. BH4, whose synthesis is rate-limited by GTP cyclohydrolase, is a particularly important cofactor, because in its absence, eNOS can generate superoxide anion. Fourth, homodimerization of eNOS may be interrupted. Dimerization of eNOS and its proper interactions with caveolin and hsp90 are important cofactors of eNOS. Perfusion of Akt decreases eNOS activity. Sixth, NO produced by eNOS may be rapidly inactivated by reaction with superoxide (O2−) to form peroxynitrite (ONOO−). This superoxide can be formed by NAD(P)H oxidase, or uncoupled eNOS. Peroxynitrite is itself a strong oxidant that can damage tissues. Peroxynitrite also nitrosylates tyrosine residues in proteins, a finding by Beckman et al that allows immunohistochemical staining for nitrotyrosine to be used as a surrogate marker for the presence of peroxynitrite. These mechanisms are not mutually exclusive, and each of them has been demonstrated in vivo.

Phosphorylation of eNOS at S1179 by Akt kinase appears to be an important step in the regulation of its activity. S1179 phosphorylation activates eNOS, increasing its enzymatic activity and reducing dependence on intracellular calcium. The protective effects of estrogen act in part through increasing eNOS S1179 phosphorylation. Recent work indicates that PPARy, leptin, and adiponectin also modulate eNOS S1179 phosphorylation.

Molnar et al examined 2 potential mechanisms for endothelial dysfunction in the mice fed the high fat and sucrose diet: eNOS phosphorylation, and eNOS dimerization. Western blot analysis showed that Akt phosphorylation and eNOS S1179 phosphorylation were relatively unaffected by the high-fat and sucrose diet, although there were some minor variations between vascular beds. Thus, in this model at least, abnormalities in eNOS phosphorylation do not appear to account for endothelial dysfunction. Rather, the authors found that eNOS dimerization was nearly absent in the mice fed the high-fat and sucrose diet. In addition, an increase in

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Circulation Research is available at http://www.circresaha.org
DOI: 10.1161/01.RES.0000170705.56583.45
Mechanisms of endothelial dysfunction

arterial nitrotyrosine staining suggested an increase in peroxynitrite levels in these animals, providing a possible mechanism for inhibition of dimerization.

Endothelial dysfunction is an early step in atherogenesis, and may occur before structural changes in the vasculature. Later steps include vascular injury, accumulation of lipid into foam cells, oxidation of LDL, and the recruitment of inflammatory cells, resulting in development of plaques. Molnar et al subjected the diabetic mice to femoral artery denudation, to assess neointimal proliferation in response to vascular injury. This model allows the vascular injury response to be quantitated and studied separately from atherosclerotic lesion formation. Mice fed the high-fat and sucrose diet did not show an increase in lesion formation, but actually showed a reduction in lesion burden compared with mice fed a normal diet. This unexpected result underscores that the links between diabetes and atherogenesis are complex, and are not limited to endothelial dysfunction. It shows that endothelial dysfunction can be separated from vascular injury response, and that the former is worse in the high-fat diet fed mice, while the latter is less severe. Although endothelial dysfunction is likely involved in the pathogenesis of arteriosclerosis, this model of diabetes may require additional factors, such as hyperlipidemia or hypercoagulability, to manifest abnormalities in later steps in atherogenesis.

This study is an important step in unraveling the complex links between metabolism and vascular abnormalities. The metabolic syndrome is a clinical constellation of glucose intolerance and insulin resistance, obesity, hypertension, hyperlipidemia, inflammation, and hypercoagulability. It is likely that the metabolic changes seen in diabetes, obesity, and metabolic syndrome together induce changes in the vasculature that result not only in endothelial dysfunction, but also increased propensity to vascular injury and atherogenesis. It remains to be seen how this model compares with other mouse models of diabetes and obesity, for example ob/ob mice (which lack leptin), db/db mice (which lack the leptin receptor), or mouse models of type I diabetes that use islet cell toxins such as streptozotocin or alloxan. Future studies will likely involve combining mouse models of diabetes, such as this one, with other mouse models that provide the additional factors of hyperlipidemia or hypercoagulability, such as Western diet-fed apoE knockout mice or LDL receptor knockout mice.

Acknowledgments

P.L.H. is supported by PHS grants HL057818, NS33335, NS048426, and NS010828.

References


Key Words: diabetes, obesity, hypercoagulability, hyperlipidemia, hypertension
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Circ Res. 2005;96:1129-1131
doi: 10.1161/01.RES.0000170705.56583.45
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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