Diabetes-Accelerated Atherosclerosis and Inflammation

To the Editor:

We read with interest the Letter to the Editor by Marfella et al1 in response to our review article on the role of glucose and lipids in diabetes-accelerated atherosclerosis.2 Marfella et al2 point out that inflammation is likely to play important roles in diabetes-associated cardiovascular events. Indeed, in our review article,2 we highlighted recent data suggesting that both elevated glucose and lipids contribute to increased inflammation. There is increasing evidence that type 1 and type 2 diabetes are associated with an enhanced inflammatory state and that inflammatory cells contribute to atherosclerotic lesion initiation and lesion disruption.

Accordingly, type 1 diabetes can cause increases in several circulating inflammatory markers, such as C-reactive protein, soluble intercellular adhesion molecule, CD40 ligand, interleukin (IL)-6, and S100A9.3–5 In addition, type 1 diabetes can promote a proinflammatory state in macrophages, associated with elevated IL-6, IL-8, IL-1α, and CCL2.3–4,6 Given the inflammatory basis of atherosclerosis, these findings suggest that type 1 diabetes may accelerate atherosclerosis, in part, by stimulating inflammatory monocytes and/or systemic inflammatory mediators. Indeed, intense insulin therapy results in a coordinated reduction in circulating inflammatory markers and reduced risk for cardiovascular complications.7 Furthermore, type 1 diabetes might stimulate accumulation of highly inflammatory macrophage populations in atherosclerotic lesions. In a mouse model of type 1 diabetes–accelerated lesion disruption, S100A9 is upregulated in monocytes/macrophages.8 S100A9 has recently been shown to be a marker of acute coronary syndromes in humans, further supporting an augmented inflammatory state contributing to cardiovascular disease in type 1 diabetes.9

Likewise, circulating markers of inflammation, as well as monocytic gene expression of proinflammatory mediators are elevated in type 2 diabetes.5,10 Furthermore, the presence of inflammatory macrophages in adipose tissues in states of insulin resistance and type 2 diabetes has attracted recent interest. Saturated fatty acids released from adipocytes, such as palmitate, stimulate proinflammatory cytokine release from macrophages, potentially mediating some of the inflammation associated with both obesity and type 2 diabetes.11 Interestingly, recent data suggest that inflamed visceral adipose tissues might stimulate development of atherosclerosis.12 In this context, the hypothesis that increased activity of the ubiquitin proteasome pathway in inflammatory cells might play a role in mediating lesion instability associated with type 2 diabetes is interesting,13 although a causal relationship has not been established. Because diabetes and the metabolic syndrome indirectly affect all tissues in the body, a number of processes are likely to contribute to inflammation and the associated atherosclerosis.

Together, there is ample data supporting an important role for inflammation in atherosclerosis associated with both type 1 and type 2 diabetes/insulin resistance. Elevated glucose and certain lipids, such as modified lipoprotein particles or saturated fatty acids, might each contribute to the enhanced inflammation, atherosclerosis, and cardiovascular events.3–5

Sources of Funding

Research in the authors’ laboratories is supported by NIH HL62887, HL92969, and DK063159 and JDRF 5-2008-257. MMA is supported by training grant T32-HL07829.

Disclosures

None.

References


Diabetes-Accelerated Atherosclerosis and Inflammation
Jenny E. Kanter, Michelle M. Averill, Renee C. LeBoeuf and Karin E. Bornfeldt

*Circ Res.* 2008;103:e116-e117
doi: 10.1161/CIRCRESAHA.108.182642
*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
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:
http://circres.ahajournals.org/content/103/8/e116

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* 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 *Circulation Research* is online at:
http://circres.ahajournals.org//subscriptions/