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 pointed 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 monocytes, 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 monocyte populations 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 monocyte 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.2,10

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Disclosures

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References


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