Diabetes, Ubiquitin Proteasome System and Atherosclerotic Plaque Rupture

To the Editor:

We read with interest the review of Kanter and coworkers about the role of glucose and lipids on atherosclerotic lesion initiation or progression to advanced plaques.1 He pointed out that hyperglycemia alone appears insufficient to accelerate atherosclerosis, at least in various animal models. He adds that little is still known about the role of diabetes in accelerating cardiovascular events merely by inducing an accelerated progression of atherosclerotic lesions. Finally, he concludes that studies on advanced lesions will be necessary to further our knowledge on the cellular and molecular mechanisms whereby diabetes leads to cardiovascular events. This gap in knowledge, reducing the role of the hyperglycemia on atherosclerosis progression toward plaque rupture, may limit the therapeutic strategy to reduce the impact of diabetes on cardiovascular events. In recent years, it has been firmly established that inflammation contributes to plaque rupture and cardiovascular events.2 Several inflammatory markers have been identified in atherosclerotic lesions. Among them are cytokines and growth factors, which are released by activated macrophages that, together with T cells, are major cellular components in atherosclerotic lesions.3 However, the inflammatory burden linked to diabetes may contribute to plaque rupture and cardiovascular disease (CVD).4 A thin fibrous cap and a large lipid core in association with inflammatory cell infiltration and necrotic areas, apoptosis of vascular cells (VSMC), decrease in collagen production, and increase in collagen degradation are key characteristics of the unstable atheroma.5 In atherecтомy specimens, the cell-rich and necrotic areas are increased in de novo lesions in persons with diabetes.4 In a series of coronary arteries examined after sudden death, the extent of the necrotic core of plaques, calcification, and healed ruptures were increased in patients with type 2 diabetes.4 Moreover, atherosclerotic lesions from diabetic patients were characterized by higher apoptosis of VSMC, higher nuclear factor-kappa B (NF-κB) activation and metalloproteinases-9 (MMP-9) levels along with a lesser interstitial collagen content.5 So, all this might increase the risk of future acute ischemic events precipitated by inflammatory-dependent rupture of atherosclerotic plaques. Moreover, it is well recognized that inflammation is one manifestation of oxidative stress and the pathways that generate the mediators of inflammation, such as adhesion molecules and interleukins, are all induced by oxidative stress.6 Although these processes can be potentiated by diabetes and can contribute to the plaque rupture the molecular mechanisms linking inflammation and oxidative stress with CVD in diabetic plaques are not fully clarified.

However, emerging evidence suggests that the ubiquitin-proteasome system (UPS) may play a role in the development of plaque instability in diabetic atherosclerosis. The UPS, the major pathway for nonlysosomal intracellular protein degradation in eucaryotic cells, is activated by oxidative stress, and it is required for activation of NF-κB by degradation of its inhibitory IκB proteins.7 In this context, recent data suggest an interesting mechanism by which hyperglycemia-induced oxidative stress, increasing ubiquitin-proteasome activity, may mediate inflammatory activity in diabetic atherosclerotic plaques. Macrophages, T-lymphocytes and HDL-DR+ inflammatory cells were more abundant in diabetic than in nondiabetic plaques and represented the major source of ubiquitin-proteasome activity, suggesting the presence of an active inflammatory reaction in diabetic lesions.8 Concomitantly higher expression of ubiquitin and proteasome has been evidenced in human plaque macrophages obtained from the asymptomatic carotid lesions of patients with type 2 diabetes compared with nondiabetic lesions. In agreement with the difference in ubiquitin-proteasome staining pattern, the histological milieu of the lesions appears different with regard to cellularity, but not in the degree of vessel stenosis, suggesting that diabetic and nondiabetic lesions are only different as regard to inflammatory burden. Of note, it has been shown that oxidative stress can stimulate the UPS in macrophages by inducing the expression of components of its enzymatic machinery such as ubiquitin-binding proteins.9 Accordingly, in cultured monocytes from diabetic patients it has been evidenced that O2 production as well as ubiquitin-proteasome activity and NF-κB levels were significantly higher when compared with nondiabetic patients. Thus, it has been proposed that increased ubiquitin-proteasome activity in plaque macrophage, as consequence of oxidative stress overexpression, may enhance the synthesis of NF-κB in the same cell, possibly representing a crucial step in the pathophysiology of diabetic plaque instability. In line with this construct, the observations that the ubiquitin-proteasome activity was greater in diabetic atherosclerotic lesions as compared with nondiabetic lesions, and was associated with higher NF-κB and MMP-9 levels along with a lesser interstitial collagen content, suggest that this system may have an important role in the inflammatory process of atherosclerotic plaques of type 2 diabetic patients.

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References


