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Inflammation and Cardiovascular Disease in Diabetes

Patients with type 1 and type 2 diabetes have 2–4-fold higher risk of having heart disease or stroke contributing towards shorter life expectancy as compared to those without diabetes [1, 2]. In the Swedish National Diabetes Registry, patients with type 1 diabetes diagnosed before the age of 10 years had a 30-fold higher risk of coronary heart disease and acute myocardial infarction occurring in their early adult years compared to people without diabetes [3]. Coronary artery atherosclerosis in diabetes is more diffuse with greater inflammatory infiltrate and larger necrotic core size [4]. In addition to coronary artery disease, diabetes increases risk of cardiomyopathy, impaired cardiac remodeling post-myocardial infarction, heart failure, ischemic stroke and sudden cardiac death. Both hyperglycemia and hyperinsulinemia/insulin resistance are implicated in the pathogenesis of cardiovascular disease in diabetes [5]. In this comprehensive review [6], we have described several of the mechanisms underlying these diseases. The prolonged increases in reactive oxygen species (ROS) appears to be the common element upstream in diabetic cardiovascular cells. Intracellular hyperglycemia causes excessive ROS production which activates several damaging pathways downstream leading to cellular injury. This activates nuclear poly(ADP-ribose) polymerase, which inhibits GAPDH, shunting early glycolytic intermediates into pathogenic signaling pathways. ROS and poly(ADP-ribose) polymerase also reduce sirtuin, PGC-1α, and AMP-activated protein kinase activity. These changes cause decreased mitochondrial biogenesis, increased oxidative stress, and disturbed circadian clock synchronization of glucose and lipid metabolism. Physiological levels of ROS are required for normal homeostasis but levels too high, for too long or at abnormal locations lead to cardiovascular diseases. In the study by Jannat et al. published in this issue, the authors measured oxidative stress markers in 157 patients with type 2 diabetes and 50 participants without diabetes. Oxidative stress markers included measurement of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), myeloperoxidase (MPO) activity, lipid peroxides such as malondialdehyde (MDA) and total oxidative stress (TOS). The neutrophil-to-lymphocyte ratio (NLR) also reflects the presence of oxidative stress. The authors found that patients with diabetes had higher levels of all markers of oxidative stress compared to people without diabetes. None of the subjects included in the study had cardiovascular disease and very few had microvascular complications. Whether elevated plasma markers of oxidative stress correlated with future cardiovascular disease could not be studied due to cross-sectional nature of this study. However, the successful reduction in CVD events in the colchicine (LoDoCo) and CANTOS clinical trials have highlighted the role of inflammasomes and their major product IL-1ß [7–10]. In patients with established CAD, anti-inflammatory drug colchicine was shown to reduce CRP concentrations on a background of statin and aspirin therapy though this was not seen in the LoDoCo-MI trial in the post-acute MI phase [10, 11]. In the CANTOS trial, canakinumab, an interleukin (IL)-1ß neutralizing monoclonal antibody significantly reduced hs-CRP, IL-6 levels and MACE events in patients with MI without significant LDL reduction. In the study, patients with higher hs-CRP reduction after first dose of canakinumab

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showed greater reduction in MACE events. About 40% of the study population (4,057 individuals) had diabetes at baseline, 50% had prediabetes and 10% had normoglycemia [12]. Interestingly, similar relative risk reduction of cardiac events was observed across the spectrum of dysglycemia. However, in animal models, hyperglycemia-induced oxidative stress induced activation of NLRP3 and AIM2 inflammasomes in myeloid cells promoting atherosclerotic lesions. While in humans, mutations promoting clonal hematopoiesis were shown to promote inflammasome activation thereby increasing the risk of coronary artery disease [13]. Moreover, Jaiswal et al reported a 1.3-fold increased odds of clonal hematopoiesis of indeterminate potential (CHIP) in patients with diabetes [14]. Further studies are ongoing in this exciting field of research to understand diabetic cardiovascular disease better.

In addition to diabetes, abnormal weight gain leads to a state of chronic unresolved systemic inflammation which is known to be an independent risk factor for cardiovascular disease. Particularly, dysfunctional adipose tissue plays a central role in insulin resistance and dyslipidemia leading to increased CVD. Adiponectin, an anti-inflammatory adipokine, is inversely proportional to BMI and in particular, visceral adipose tissue [15]. Plasma adiponectin levels were lower in patients with acute coronary syndrome whereas higher plasma concentrations are thought to decrease the risk of CVD in men with and without diabetes [16–18]. Suggested mechanisms mediated by adiponectin in CVD include decreased NF-Kb signaling and NADPH oxidase activity, increased AMPK and AKT signaling and increased eNOS phosphorylation and coupling [19]. In this issue, Soliman and colleagues studied adiponectin levels and insulin resistance in 65 children and adolescent patients with type 1 diabetes. In this cross-sectional cohort study conducted in Egypt, 77% patients had low level of estimated glucose disposal (eGDR) which was related to higher insulin resistance while 23% had normal levels of eGDR. 40% patients had low serum adiponectin with mean value of 2.4 +/– 3.6 ng/mL. Patients with low serum adiponectin had a higher BMI. There was a significant association between adiponectin levels and dyslipidemia and occurrence of microalbuminuria but no correlation between the levels of adiponectin and insulin resistance was observed. This could be due to the small number of patients in the study. However, this study highlights the very important problem of childhood obesity especially in patients with early onset of type 1 diabetes. In addition to prolonged hyperglycemia, adipose tissue inflammation and insulin resistance due to abnormal weight gain poses a greater risk to cardiovascular disease and calls for early intervention.

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