

Preface

Diabetes has a profoundly deleterious effect on the cardiovascular system. However, the pathophysiologic mechanisms, which commence even before the blood glucose threshold for diagnosis of diabetes is reached, are not well understood. Elucidation of these mechanisms is critically important to developing appropriate prevention and therapeutic strategies. The purpose of this edition of the *Endocrinology and Metabolism Clinics of North America* is to shed light on these multiple and complex mechanisms. Hypertension, dyslipidemia, hyperglycemia, and endothelial dysfunction are all key components of the metabolic syndrome. Hypertension exacerbates all macro- and microvascular complications of diabetes, and there is evidence of increased sensitivity to the renin-angiotensin-aldosterone system (RAAS) in diabetes, particularly in type 2, because adipose tissue is a source of the angiotensin II precursor, angiotensinogen. In this issue, Jandeleit-Dahm and Cooper discuss evidence that RAAS inhibition attenuates diabetes complications and focus on new approaches to inhibiting this key system. Cahil and Ginsberg present a comprehensive analysis of lipoprotein metabolism in patients with type 1 and type 2 diabetes compared with normal subjects, and they suggest that overproduction of very low-density lipoprotein is a central feature leading to lower high-density lipoprotein cholesterol levels and more small, compacted low-density lipoprotein cholesterol, which is highly atherogenic because of its propensity toward oxidation. Yan and colleagues discuss evidence that glucose promotes cardiovascular complications by the formation of advanced glycosylation end products (AGEs) that promote inflammation, oxidation, and alter protein function and cell signaling pathways to damage tissues. They highlight the protective effects of blocking the AGE receptor (RAGE) using soluble RAGE. Schwartz and Reaven expand on the role of alterations in key cell signaling pathways and the critical

intersection of these alterations with oxidative stress, leading to a complex network of vascular injury. They discuss novel approaches to correct these alterations. The endothelium is a major protector of the vasculature. Hartge and colleagues discuss detailed mechanisms by which the endothelial barrier is destroyed in insulin resistance and diabetes and how activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ) may protect the endothelium. Finally, Blaschke and colleagues amplify the discussion of the potential vasoprotective effects of PPAR γ ligands, focusing on mechanisms of protection as well as side effects of the ligands.

The heart is also a key target of damage in diabetes. Fonarow and Srikanthan define diabetic cardiomyopathy and discuss in detail the mechanisms of cardiac damage in diabetes. Many of the mechanisms that damage the heart are the same as those that damage the vasculature, but also include widespread microangiopathy and autonomic neuropathy. These authors highlight the clinical presentation of diabetic cardiomyopathy and discuss recommended and potential novel therapies. Cesario and colleagues focus on a topic that is important, however infrequently discussed—channel alterations in diabetic cardiomyopathy. They discuss altered calcium homeostasis and how current and newly proposed therapies may improve these alterations.

This issue concludes with a focus on populations vulnerable to cardiovascular disease. Dave and Kamdar comprehensively review data on the influence of ethnicity on the risk of developing diabetes and diabetes associated cardiovascular disease. Of note, non-Hispanic Whites generally have lower rates of obesity and metabolic syndrome, but higher rates of diabetic heart disease. An increasingly important, but complex issue in women is polycystic ovarian syndrome (PCOS). Srikanthan and colleagues discuss pathophysiology of the hormone abnormalities and their relationship to hyperinsulinemia and insulin resistance. Finally, they outline potential mechanisms leading to increased cardiovascular disease risk and approaches to prevention and treatment of the same.

Despite several decades of promising research, cardiovascular disease remains the number one cause of mortality in men and women in the United States. Thankfully, there is widespread public recognition of the importance of factors involved in cardiovascular disease prevention (as first illustrated by the Framingham study). However, this issue of *Endocrinology and Metabolism Clinics of North America* highlights the contribution of several different events (such as hypertension, dyslipidemia, formation of advanced glycosylation end products and endothelial dysfunction) accompanying and leading to glucose intolerance, and of related conditions (such as diabetic cardiomyopathy and PCOS) to cardiovascular risk. Additionally, in a multi-ethnic society such the United States today, it is of vital importance to recognize the effect of race on cardiovascular disease risk. Hence, as we face an epidemic of obesity and type 2 diabetes, it is imperative that we reflect on

how knowledge of these factors should alter and improve our approach to cardiovascular disease prevention and therapy.

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