

Foreword



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Understanding the relationship between impaired glucose tolerance and cardiovascular disease is clearly of paramount importance to internists, endocrinologists, and cardiologists for academic as well as practical reasons. Nobody is better qualified to deal with these issues than Willa Hsueh and her colleague Preethi Srikanthan, who have assembled a number of excellent reviews for this issue.

Eric Schwartz and Peter Reaven discuss the cellular mechanisms involved in the effects of insulin resistance on vascular cells. Insulin resistance is commonly associated with hyperglycemia and elevated free fatty acids, which can stimulate signaling pathways involved in the disease process affecting vascular smooth muscle cells (VSMCs), including nuclear factor kappa B (NF- κ B), protein kinase C, and mitogen-activated protein kinase (MAPK). Reactive oxygen species (ROS) production may play a central role in the negative effects on VSMCs. These authors also address the effects of inflammation in different organs, such as fat, with release of adipocytokines that may initiate many of these deleterious effects.

The formation of advanced glycosylation end products (AGE), especially proteins, their interaction with the AGE receptor (RAGE) for these altered proteins, and their role in diabetic complications are discussed by Ann Marie Schmidt and colleagues. Although hyperglycemia is the primary cause of increased AGE products, the effects of AGE products on VSMCs include ROS production and upregulation of the expression of VCAM-1 and activation of NF- κ B, all regulators of VSMC disordered function that potentially result in the vascular complications associated with hyperglycemia.

Diabetic dyslipidemia is clearly a cause of cardiovascular complications. Chahil and Ginsburg describe in detail normal lipid homeostasis as well as the abnormalities that occur in diabetes, focusing on type 2 diabetes but also indicating the abnormal changes seen in type 1 diabetes. As they point out, the major abnormality is overproduction of very low-density lipoprotein cholesterol, which accounts for the hypertriglyceridemia and low high-density lipoprotein levels that are commonly seen in patients with type 2 diabetes. They also address management, and stress that statins and fibrates are important therapeutic agents, but add that niacin is extremely useful, especially if the hyperglycemia is adequately controlled.

Unger and colleagues introduce their article with a discussion of the normal function of the endothelial cell, followed by an exploration of the abnormalities seen in diabetes as a result of metabolic disorders and inflammatory changes that are now commonly associated with obesity and diabetes. A central theme is the importance of nitric oxide, a molecule important in endothelial function and dysfunction. Endothelial dysfunction is characterized by reduced vasodilatation, a pro-inflammatory and a pro-thrombotic state. The authors also present evidence that thiazolidinediones maybe useful in correcting endothelial dysfunction and in reducing cardiovascular abnormalities in diabetics.

As described by Cooper and colleagues, the renin-aldosterone system (RAS) plays a central role in diabetes and its complications. Hypertension is extremely common in diabetic patients and has been attributed to the effects of insulin on renal salt handling, on the VSMCs via MAPK, and on the sympathetic nervous system. On the other hand, the RAS may play a role in increasing insulin resistance. Numerous studies have demonstrated that inhibition of the RAS using either angiotensin-converting enzyme (ACE) inhibition or angiotensin II receptor blockers is a powerful means of treating hypertension in diabetics, retarding diabetic nephropathy, and even preventing or delaying the development of type 2 diabetes in patients with impaired glucose tolerance. Whether these agents also retard retinopathy is as yet unclear, but ongoing clinical trials may yet prove this important function.

The relationship between diabetes and macrovascular complications including coronary artery disease is well recognized. Less well recognized is the entity of diabetic cardiomyopathy, an important cause of heart failure in these patients, discussed in the article by Gregg Fonarow and Preethi Srikanthan. The underlying pathophysiology is thought to include micrangioathy, autonomic neuropathy, and metabolic factors described in the earlier articles. Most important, the authors point out, are the therapeutic options that include the use of beta blockers and ACE inhibitors with concomitant glycemic control.

David Cesario, Ramandeep Brar, and Kalyanam Shivkumar describe the underlying mechanisms involved in diabetic cardiomyopathy, namely, the role of ion channels and altered calcium homeostasis. They hypothesize that in addition to the standard therapies, insulin-like growth factor-1 maybe a useful

therapeutic agent, inasmuch as it has been shown experimentally to restore normal calcium homeostasis in diabetic cardiomyocytes, prevent the decline in sarco/endoplasmic reticulum CA^{2+} ATPase levels, promote cardiac growth, increase cardiac contractility, and increase cardiac output and ejection volume.

The influence of ethnicity on diabetic complications is extremely important, and Jatin Dave and Vikram Kamdar address the role of ethnicity in diabetic heart disease. Obesity, metabolic syndrome, impaired glucose tolerance, and diabetes are common in African Americans, Hispanic Americans, and Native Americans, and are becoming a problem in Asian Americans. Genetics is an obvious element in this high incidence of these various metabolic abnormalities, as well as environmental factors, and thus, studying the ethnic variations in predisposing factors to diabetic complications is an essential component for disease prevention and treatment.

Polycystic ovarian syndrome (PCOS) is a common cause of infertility but is also a classic example of hyperinsulinemia and insulin resistance. Therefore, Preethi Srikanthan, Stanley Korenman, and Susan Davis discuss the possibility that PCOS predisposes to cardiovascular complications. Although the evidence is gradually accumulating, it is important to consider this complication and treat the disorder appropriately both from a menstrual and infertility aspect and from the aspect of insulin resistance and its predictable outcomes. Metformin and thiazolidinediones have been shown in clinical trials to be effective in treating both aspects.

Willa Hsueh and colleagues summarize the effects of thiazolidinediones on the vasculature in diabetics. Experimental and clinical studies have demonstrated the value of these agents, not just as insulin sensitizers and in improving glucose homeostasis but also as protective to the vasculature at various stages of the disease process. The data suggest that some of the effects may be via insulin sensitivity and others may be directly on the inflammatory process that is commonly seen in obesity and type 2 diabetes. From many aspects, these agents have found an important role in managing diabetes and in preventing the deterioration of the cardiovascular complications.

This issue has focused on one major complication of diabetes, a common and devastating disease, and the issue editors and authors are to be commended for their focused articles that will ensure easy reading and a comprehensive reference for all practitioners.

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