

## Preface



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*Guest Editors*

Why a comprehensive review on metabolic syndrome so many years after recognition of this disorder as a worldwide epidemic? As we gain better understanding of underlying mechanisms of the syndrome, tailored treatment modalities based on pathophysiology are of paramount importance to general internists, endocrinologists, cardiologists, hepatologists, ob-gyns, and everyone involved in the care of patients with metabolic syndrome. Pi-Sunyer opens this issue of the *Medical Clinics of North America* with a critical review of the various definitions of metabolic syndrome that have been proposed by different organizations. Definitions have come closer over the years, and we hope to arrive at one unifying criterion that best helps to identify patients at risk for diabetes and coronary heart disease. Controversy over the validity of the syndrome itself is eloquently discussed by Brietzke. He speculates that insulin resistance may be “yet another spoke in the wheel of syndrome,” but the actual “hub may prove to be the visceral adipocyte producing the inflammatory adipokines and free fatty acids.” He proposes that “the toxic fat syndrome” may more accurately describe the state of the proinflammatory condition.

The basic pathophysiologic mechanism underlying insulin resistance is discussed by Lann and LeRoith. Metabolic syndrome is exacerbated by abnormal insulin signaling/secretion, impaired glucose disposal, lipotoxicity, and proinflammatory cytokines. Early-stage beta cell dysfunction manifests as a loss of first-phase insulin secretion leading to eventual hyperinsulinemia, resulting in insulin receptor downregulation and the insulin-resistant state. A mixture of various adipokines contributes to the modulation of

hypertension and to endothelial dysfunction. Primary prevention of metabolic syndrome requires modification of the lifestyle that leads to this toxic state. Wyatt leads a national patient education program to improve metabolic syndrome through a behavioral modification program. Despite high recidivism in weight reduction, successful strategies on a national level are critical to halting this epidemic.

The challenge of preventing type 2 diabetes with metabolic syndrome is discussed by Tupper and Gopalkrishnan. Treatment targeting the root cause of insulin resistance would not only delay the onset but might also reduce the overall risk. Prevention in the true sense, however, may require more long-term study. For those with type 2 diabetes, Joffe and Yanagisawa review new strategies that are currently available for achieving glycemic control while at the same time minimizing weight gain and the complications associated with it. Incretin mimetics, a new class of diabetes medications, including the GLP-1 receptor agonists and the DPP-4 enzyme inhibitors, has some advantages in this regard. These medications may have the added benefit of causing beta cell neogenesis and proliferation, thus slowing the progression of beta cell failure that occurs in the type 2 diabetic.

The hepatic manifestation of metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), is the leading cause of chronic liver disease in the Western world. Abdelmalek and Diehl discuss whether NAFLD is due to insulin resistance in the liver or is the result of systemic insulin resistance. They demonstrate that like adipose tissue, fatty hepatocytes produce circulating factors such as TNF-alpha and IL-6, contributing to systemic insulin resistance. Polycystic ovarian syndrome (PCOS) is an ovarian manifestation of metabolic syndrome leading to hyperandrogenism. Magnotti and Futterweit review the pathophysiology and clinical manifestations linked to ovarian insulin resistance. Treatment recommendations based on disease mechanism are discussed for both NAFLD and PCOS.

The definition of metabolic syndrome for risk assessment of cardiovascular morbidity and mortality has been questioned. Obunai, Jani, and Daggas conclude that although compared to a Framingham Risk Score, diagnosis of metabolic syndrome proved less sensitive at predicting cardiovascular events, recognition of metabolic syndrome is complementary to the calculation of a Framingham Risk Score.

Directly linked to cardiovascular risk and endovascular disease is the dyslipidemia triad of increased triglyceride, decreased HDL, and increased small dense LDL. Smith reviews the mechanism of dyslipidemia with insulin resistance, in which an increase in free fatty acids leads to a decrease in the core lipid content of LDL, resulting in smaller particles. Smaller LDLs are more readily taken into vascular subendothelial space, and increase atherogenesis. Standard measures of LDL levels may underestimate the risk of atherogenesis in metabolic syndrome.

Suzuki and Homma describe the role of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers for hypertensive patients

with metabolic syndrome. The effect on the renin–angiotensin system blockade effect goes beyond diabetes mellitus and may be beneficial for patients with impaired glucose tolerance. Aggressive blood pressure control is recommended with high-risk metabolic syndrome.

To reduce the underlying cause of metabolic syndrome, weight reduction with diet and exercise is critical. To enhance such behavioral modification efforts, Bray offers his critical assessment of the current options and future hopes for pharmacological therapy. Kini, Herron, and Yanagisawa review bariatric surgery as an alternative treatment option for high-risk individuals who fail noninvasive treatment measures. A closer look into the pathophysiological mechanism of bariatric surgery as incretin-modulating surgery may lead to future noninvasive treatment options targeting the root cause of metabolic syndrome.

This issue highlights the current understanding of pathophysiology, as well as ongoing controversies. The authors are to be commended on their excellent focused reviews of the various aspects of metabolic syndrome. This comprehensive review will help us tackle the ongoing obesity epidemic with an evidence-based approach.

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