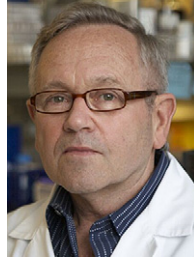


Foreword



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This is the first of two very informative issues on obesity that cover the etiology-related conditions with this growing problem that is a worldwide phenomenon.

The metabolic syndrome that includes obesity, hypertension, hyperlipidemia, and glucose intolerance has insulin resistance as the underlying cause and is commonly seen in patients with type-2 diabetes. As described in the article by Gallagher, LeRoith, and Karnieli, it is extremely common in both developed countries as well as in third world countries, and it is associated with visceral adiposity. Though the exact definitions of the metabolic syndrome differ slightly between various organizational and governing bodies, its existence and its relationship to type-2 diabetes are unequivocal. The article also presents the experimental evidence, upon which the insulin resistance is caused by the obesity and how the insulin resistance causes the hypertension, hyperlipidemia, and glucose intolerance.

Gerald Reaven, one of the investigators who described the metabolic syndrome (he originally named it syndrome “X”), describes the relationship between obesity and cardiovascular disease. He initially presents the relationship between abdominal obesity and reduced insulin-mediated glucose uptake into muscle. The resultant insulin resistance and hyperinsulinemia lead to increased risk factors for cardiovascular disease. Today, this cardio-metabolic syndrome is so common that major efforts are underway to attempt to reverse the abnormality, since heart attacks and strokes are the major causes of the high mortality rates in type-2 diabetic patients.

Razani, Chakravarthy, and Semenkovich describe the basic and clinical effects of insulin resistance on the cardiovascular system—how insulin resistance causes atherosclerosis by way of hyperlipidemia and inflammation. They also outline experimental evidence invoking NF κ B, JNKinase, and oxidative stress in this process. They describe the various ways of preventing the atherosclerosis, such as angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers (ARBs), and statins, and present results of clinical trials that have utilized PPAR α and PPAR α agonists, but they point out that the latter trials have been rather disappointing.

Obesity and hyperlipidemia is another complication that is commonly appreciated in the medical community. The cardiovascular risk associated with obesity is mostly predicted by the hyperlipidemia, characterized by increased triglyceride levels, decreased high-density lipoproteins (HDL) levels, and a shift in low-density lipoproteins (LDL) to a more pro-atherogenic composition (small dense LDL). These features are covered in the article by Franssen, Monajemi, Stroes, and Kastelein. They describe how the classic concept of insulin resistance and lipolysis, with excess FFA release leading to hypertriglyceridemia, is still the central theme. However, newer concepts, such as the hypothalamic control of lipid metabolism, are undoubtedly important and may allow for the development of newer therapeutic agents.

Obesity is associated with increased free fatty acids, inflammation, and insulin resistance. Insulin resistance in adipocytes leads to increased lipolysis. One of the conundrums is what precedes and what the consequence is. Boden, in his scholarly article, describes how free fatty acids (FFAs) can induce or worsen insulin resistance at the cellular level in many metabolically important tissues, an effect called “lipotoxicity.” He also describes how different medications, including fibrates, TZDs and the experimental agent Acipimox (a nicotinic analog), can reverse the situation, but points out that the insulin resistance, whether induced by FFAs or inflammation, is best reversed by weight loss.

Obesity-related hypertension has many causes, as outlined by Kurukulasuriya, Stas, Lastra, Manrique, and Sowers. These include well-known causes such as insulin resistance, activation of the renin-angiotensinogen-aldosterone system with renal sodium retention, and the sympathetic nervous system. More recent studies have demonstrated that adipocytokines, FFAs, and other molecules may cause endothelial dysfunction. More recently, the effect of sleep deprivation on obesity and, therefore, on hypertension has been described. Although the causes are being investigated, the need for intensive therapy is primary to prevent the cardiovascular and renal complications that result.

The relationship between obesity and cardiovascular disease is further explored in the article by Zalesin, Franklin, Miller, Peterson, and McCullough. They address the increased risk factors and increased cardiac disease in obese individuals that cause heart attacks, atrial fibrillation, and heart failure. Importantly, they describe the epidemic of obesity and

the increased rates of hypertension, hyperlipidemia, and glucose intolerance in the pediatric population and the eventual increase in cardiovascular disease that is bound to result at younger ages.

Muniyappa, Iantorno, and Quon describe an integrated view of insulin resistance and endothelial function. The endothelium utilizes NO to affect vasodilation, a critical function in maintaining normal vasculature. NO production is also under the control of insulin action by way of the activation of Akt, and its downstream signaling pathway. Similar to the situation in classic metabolic tissues such as muscle, fat, and liver, insulin resistance in the endothelium involves inhibition of the insulin signaling cascade and reduced levels of NO, specifically in the endothelial cells. This effect may be secondary to inflammatory cytokines, FFAs, and other factors. Thus, insulin resistance and endothelium dysfunction in obesity and type-2 diabetes may be integrally related and therapies to overcome the resistance will improve both systems.

A fascinating new concept that has developed from recent studies is the role of skeletal muscle mitochondrial dysfunction in the cause of insulin resistance commonly associated with obesity and diabetes. Højlund, Mogensen, Sahlin, and Beck-Nielsen describe the defect and question whether it is of both genetic and environmental etiologies, since the alterations can often be detected prior to the onset of both obesity and diabetes. They point out, however, that exercise and diet (lifestyle changes) can partially reverse the defect, suggesting that environment is, at least partially, playing a role.

Ranadive and Vaisse cover the topic of monogenic causes of obesity. Though obesity in the general population is a polygenic disorder, monogenic disorders have helped to understand the disease. Leptin and leptin-receptor mutations have clearly established this pathway in control of appetite. Mutations in the proopiomelanocortin pathways and the melanocortin-4 receptor have extended our understanding of the condition. These single mutations that cause severe obesity represent less than 5% of the causes, but in animal and human studies have allowed the field to progress, and the signaling pathways involved have suggested new gene targets for therapy.

Until recently, the adipocyte was considered the tissue that stored triglyceride. Recent studies have demonstrated that the adipose tissue is an endocrine organ secreting a large number of adipocytokines and hormones; the exact number is still unclear. Halberg, Wernstedt, and Scherer describe exciting new information regarding adipocyte physiology. They discuss angiogenesis, the involvement of inflammation, and extracellular matrix in this tissue. Importantly, they present the information available on the adipocyte "secretome," an important component of the adipocytokine physiology.

As discussed by Jayasena and Bloom, there has been a fundamental change in our understanding of the role of gastrointestinal hormones that were considered factors primarily affecting the gastrointestinal function. Ghrelin is produced from the stomach and stimulates appetite, whereas cholecystokinin and other peptides inhibit appetite. Most

importantly, the glucagon-like peptides (incretins) that are released from the intestinal tract affect insulin and glucagon secretion from the pancreas that may affect satiety have become the focus of the pharmaceutical industry and are being used for the treatment of obese type-2 diabetics.

The reader will undoubtedly find these articles of tremendous interest and should stimulate the desire to read the second issue on obesity that will cover, amongst other topics, the latest in therapeutics.

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