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Derek LeRoith

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**The Metabolic Syndrome—from Insulin Resistance
to Obesity and Diabetes** 559
Emily Jane Gallagher, Derek LeRoith, and Eddy Karnieli

In today's society with the escalating levels of obesity, diabetes, and cardiovascular disease, the metabolic syndrome is receiving considerable attention and is the subject of much controversy. Greater insight into the mechanism(s) behind the syndrome may improve our understanding of how to prevent and best manage this complex condition.

**Insulin Resistance: the Link Between Obesity
and Cardiovascular Disease** 581
Gerald M. Reaven

Insulin-mediated glucose disposal varies at least sixfold in apparently healthy individuals. The adverse effect of decreases in the level of physical fitness on insulin sensitivity is comparable to the untoward impact of excess adiposity, with each accounting for approximately 25% of the variability of insulin action. It is the loss of insulin sensitivity that explains why obese individuals are more likely to develop cardiovascular disease, but not all overweight/obese individuals are insulin resistant. At a clinical level, it is important to identify those overweight individuals who are also insulin resistant and to initiate the most intensive therapeutic effort in this subgroup. Finally, it appears that the adverse impact of

overall obesity, as estimated by body mass index, is comparable to that of abdominal obesity, as quantified by waist circumference.

Insulin Resistance and Atherosclerosis

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Babak Razani, Manu V. Chakravarthy,
and Clay F. Semenkovich

Insulin resistance characterizes type 2 diabetes and the metabolic syndrome, disorders associated with an increased risk of death due to macrovascular disease. In the past few decades, research from both the basic science and clinical arenas has enabled evidence-based use of therapeutic modalities such as statins and angiotensin-converting enzyme inhibitors to reduce cardiovascular (CV) mortality in insulin-resistant patients. Recently, promising drugs such as the thiazolidinediones have come under scrutiny for possible deleterious CV effects. Ongoing research has broadened our understanding of the pathophysiology of atherosclerosis, implicating detrimental effects of inflammation and the cellular stress response on the vasculature. In this review, we address current thinking that is shaping our molecular understanding of insulin resistance and atherosclerosis.

Obesity and Dyslipidemia

623

Remco Franssen, Houshang Monajemi, Erik S.G. Stroes,
and John J.P. Kastelein

The alarming and still increasing prevalence of obesity and associated cardiovascular risk raises much concern. The increase in cardiovascular risk depends to a significant extent on the changes in lipid profiles as observed in obesity. These changes are decreased high-density lipoprotein cholesterol and increased triglyceride levels. Much effort has already been expended into the elucidation of the mechanisms behind these obesity-associated lipid changes. Insulin resistance certainly plays a central role and, in addition, both hormonal and neurologic pathways have recently been found to play an important role. This article focuses on the mechanisms involved in the development of the proatherogenic lipid changes associated with obesity.

Obesity and Free Fatty Acids

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Guenther Boden

Plasma free fatty acid (FFA) levels are elevated in obesity. FFAs cause insulin resistance in all major insulin target organs (skeletal muscle, liver, endothelial cells) and have emerged as a major link between obesity, the development of the metabolic syndrome, and atherosclerotic vascular disease. FFAs also produce low-grade inflammation in skeletal muscle, liver, and fat, which may contribute to cardiovascular events. The challenges for the future include the prevention or correction of obesity and elevated plasma FFA levels through methods that include decreased caloric intake

and increased caloric expenditure, the development of methods to measure FFAs in small blood samples, and the development of efficient pharmacologic approaches to normalize increased plasma FFA levels.

Hypertension in Obesity

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L. Romaine Kurukulasuriya, Sameer Stas, Guido Lastra, Camila Manrique, and James R. Sowers

Hypertension and obesity are major components of the cardiometabolic syndrome and are both on the rise worldwide, with enormous consequences on global health and the economy. The relationship between hypertension and obesity is multifaceted; the etiology is complex and it is not well elucidated. This article, reviews the current knowledge on obesity-related hypertension. Further understanding of the underlying mechanisms of this epidemic will be important in devising future treatment avenues.

Impact of Obesity on Cardiovascular Disease

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Kerstyn C. Zalesin, Barry A. Franklin, Wendy M. Miller, Eric D. Peterson, and Peter A. McCullough

The epidemiology of cardiovascular disease risk factors is changing rapidly with the obesity pandemic. Obesity is independently associated with the risks for coronary heart disease, atrial fibrillation, and heart failure. Intra-abdominal obesity is also unique as a cardiovascular risk state in that it contributes to or directly causes most other modifiable risk factors, namely, hypertension, dysmetabolic syndrome, and type 2 diabetes mellitus. Obesity can also exacerbate cardiovascular disease through a variety of mechanisms including systemic inflammation, hypercoagulability, and activation of the sympathetic and renin-angiotensin systems. Thus, weight reduction is a key strategy for simultaneous improvement in global cardiovascular risk, with anticipated improvements in survival and quality of life.

An Integrated View of Insulin Resistance and Endothelial Dysfunction

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Ranganath Muniyappa, Micaela Iantorno, and Michael J. Quon

Endothelial dysfunction and insulin resistance are frequently comorbid states. Vasodilator actions of insulin are mediated by phosphatidylinositol 3-kinase (PI3K)-dependent signaling pathways that stimulate production of nitric oxide from vascular endothelium. This helps to couple metabolic and hemodynamic homeostasis under healthy conditions. In pathologic states, shared causal factors, including glucotoxicity, lipotoxicity, and inflammation selectively impair PI3K-dependent insulin signaling pathways that contribute to reciprocal relationships between insulin resistance and endothelial dysfunction. This article discusses the

implications of pathway-selective insulin resistance in vascular endothelium, interactions between endothelial dysfunction and insulin resistance, and therapeutic interventions that may simultaneously improve both metabolic and cardiovascular physiology in insulin-resistant conditions.

Mitochondrial Dysfunction in Type 2 Diabetes and Obesity

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Kurt Højlund, Martin Mogensen, Kent Sahlin,
and Henning Beck-Nielsen

Insulin resistance in skeletal muscle is a major hallmark of type 2 diabetes mellitus (T2D) and obesity that is characterized by impaired insulin-mediated glucose transport and glycogen synthesis and by increased intramyocellular content of lipid metabolites. Several studies have provided evidence for mitochondrial dysfunction in skeletal muscle of type 2 diabetic and prediabetic subjects, primarily due to a lower content of mitochondria (mitochondrial biogenesis) and possibly to a reduced functional capacity per mitochondrion. This article discusses the latest advances in the understanding of the molecular mechanisms underlying insulin resistance in human skeletal muscle in T2D and obesity, with a focus on possible links between insulin resistance and mitochondrial dysfunction.

Lessons from Extreme Human Obesity: Monogenic Disorders

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Sayali A. Ranadive and Christian Vaisse

Human obesity has a strong genetic component. Most genes that influence an individual's predisposition to gain weight are not yet known. However, the study of extreme human obesity caused by single gene defects has provided a glimpse into the long-term regulation of body weight. These monogenic obesity disorders have confirmed that the hypothalamic leptin–melanocortin system is critical for energy balance in humans, because disruption of these pathways causes the most severe obesity phenotypes. Approximately 20 different genes and at least three different mechanisms have been implicated in monogenic causes of obesity; however, they account for fewer than 5% of all severe obesity cases. This finding suggests that the genetic basis for human obesity is likely to be extremely heterogeneous, with contributions from numerous genes acting by various, yet undiscovered, molecular mechanisms.

The Adipocyte as an Endocrine Cell

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Nils Halberg, Ingrid Wernstedt-Asterholm,
and Philipp E. Scherer

Adipose tissue contains many cell types. Among the more abundant are adipocytes, preadipocytes, immune cells, and endothelial cells. During times of excess caloric intake, these cells have to adjust and remodel to accommodate the increased demand for triglyceride storage. Based on a comprehensive analysis of the

total adipose tissue secretome, this article focuses on three areas of adipokine biology: (1) How does the adipocyte interact with the extracellular matrix over the course of obesity? (2) Does the adipocyte, per se, play a role in the innate immune response? (3) How is the angiogenic profile of adipose tissue linked to the development of insulin resistance? The authors present a comprehensive overview of all of the currently available secreted adipose tissue products that have been identified at the protein level.

Role of Gut Hormones in Obesity

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Channa N. Jayasena and Steve R. Bloom

A critical role for the gut in energy homeostasis has emerged. Gut hormones not only have a role in digestion but several of them have been found to modulate appetite in animals and humans. Current nonendocrine drugs for obesity are limited by their modest efficacies, and bariatric surgery is confined to use in severe cases. The discovery of important appetite-signaling pathways from the gut to the brain has led to the emergence of several gut hormone-derived drugs that are being investigated for clinical use. This article summarizes the physiology of the major gut hormones implicated in appetite regulation, and reviews clinical evidence that gives us insight into their potential as clinical treatments for obesity.

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