

Introduction

The prevalence of obesity is reaching staggering proportions both in the United States and worldwide and is considered a major public health issue in both developed and developing nations. In the United States, approximately one third of adults are obese,^{1,2} and another third are considered overweight; worldwide, an estimated 312 million people are classified as obese.³ Statistics from the US Department of Health and Human Services⁴ indicate that the prevalence of obesity has more than doubled in the last 40 years—from 13% in the early 1960s to ~34% in 2003–2004. These increases have been attributed to various factors, including increased calorie intake and an increasingly sedentary lifestyle.

Obesity is associated with a higher rate of mortality, with obese adults aged 50 to 71 years having a risk of death 2 to 3 times higher than adults of normal weight.⁵ Obesity is also associated with numerous cardiometabolic complications, including insulin resistance, hypertension, dyslipidemia, type 2 diabetes (DM), and cardiovascular disease (CVD). These complications are thought to be related to changes in adipose tissue metabolism that occur with obesity. Adipose tissue, once thought to be merely a site for fat storage, is an active endocrine organ that secretes hormones, cytokines, and prothrombotic and proinflammatory factors. In addition, adipocytes in obese individuals release more free fatty acids (FFAs) and less adiponectin, a cytokine with insulin-sensitizing, anti-inflammatory, and antiatherogenic properties, than do those in normal-weight individuals.⁶

Data from large population studies and small physiologic assessments have found that increased abdominal fat, particularly visceral fat, is associated with insulin resistance, type 2 DM, and hypertension. Furthermore, abdominal obesity is a strong predictor of future development of hypertension and type 2 DM, independent of body mass index.^{7–10}

In light of the importance of abdominal fat in the development of the cardiometabolic complications of obesity, it is not surprising that weight loss, particularly a reduction in waist circumference, has beneficial effects on blood pressure and insulin action and reduces the risk of developing type 2 DM and hypertension. Moderate

weight loss in obese individuals reduces total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels,¹¹ and improves blood pressure¹² and insulin sensitivity.¹³ In addition, a weight loss of ~5% reduces the risk of developing diabetes by ~60% in persons with impaired glucose tolerance.^{13,14} Weight loss also reduces the levels of markers of inflammation and inflammatory proteins in the bloodstream.¹⁵ Weight loss can be achieved with lifestyle modifications (dietary intervention and exercise), pharmacotherapy, bariatric surgery, or a combination of these modalities.

This issue of *Clinical Cornerstone* focuses on obesity and, specifically, abdominal obesity as a risk factor for cardiometabolic complications. In the first article, “Obesity-Related Cardiometabolic Complications,” Christopher P. Cannon, MD, explains how abnormalities in adipose tissue lead to cardiometabolic complications, such as hypertension, dyslipidemia, insulin resistance, type 2 DM, and CVD. Dr. Cannon clarifies the interplay between and among these conditions and sheds light on why these conditions often cluster together as part of the cardiometabolic syndrome.

It is not only the amount of fat but also the distribution of fat that is associated with the development of hypertension, insulin resistance, and type 2 DM and, hence, CVD. Sydney A. Westphal, MD, in her article “Obesity, Abdominal Obesity, and Insulin Resistance” explains why abdominal adiposity, in particular, is associated with the risk for cardiometabolic complications, and she reviews the abnormalities seen in the adipocytes of obese individuals, including increased FFA production and dysregulation of adipokine secretion.

Adiponectin is an adipocyte-derived cytokine with insulin-sensitizing, antiinflammatory, and antiatherogenic properties. Obese persons tend to have lower plasma adiponectin concentrations than do lean persons. Weight loss increases adiponectin levels, which likely contributes to the beneficial metabolic effects observed with successful weight management. James R. Sowers, MD, in his article “Endocrine Functions of Adipose Tissue: Focus on Adiponectin” clarifies the various biologic functions and properties of adiponectin and reviews nonpharmacologic and

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pharmacologic strategies to increase the inappropriately low levels of adiponectin in obese individuals.

Weight loss improves many of the medical complications associated with obesity.^{16,17} Even a modest weight loss of 5% can improve glycemic control in patients with type 2 DM¹⁸ and prevent the onset of diabetes in high-risk individuals.^{13,19} Insulin sensitivity appears to be directly related to percentage of weight loss, and improvement likely continues until a loss of ~30% of initial body weight is achieved.^{18,20} Weight loss, therefore, is a key therapeutic goal in the management of obesity complications. In the article “Fundamentals of Cardiometabolic Risk Factor Reduction: Achieving and Maintaining Weight Loss with Pharmacotherapy or Bariatric Surgery,” Elisa Fabbrini, MD, and I review the surgical and pharmacologic options available to induce weight loss when dietary and lifestyle interventions are not successful. These options include bariatric surgery (particularly, Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding) and the weight loss medications approved for long-term use by the US Food and Drug Administration—sibutramine and orlistat. We also briefly discuss a new class of agents used for weight loss, which are endocannabinoid receptor antagonists (or inverse agonists).

The endocannabinoid system (ECS) is a neuromodulatory system involved in the regulation of energy balance, eating behavior, and metabolism via central and peripheral mechanisms. Evidence from animal and human studies demonstrates that selective antagonism of G-protein-coupled cannabinoid receptors reduces body weight and improves plasma lipids and insulin action. In their article “The Endocannabinoid System as a Target for Obesity Treatment,” Louis J. Aronne, MD, Gary D. Foster, PhD, Uberto Pagotto, MD, PhD, and Stephen N. Davis, MD, FRCP, provide insight into the rationale for targeting the ECS for obesity treatment and review clinical trial data on the 2 endocannabinoid receptor antagonists—rimonabant and taranabant—that have been studied in randomized clinical trials in obese subjects.

It is hoped that this educational supplement will help clarify the relationship between abdominal obesity and its

cardiometabolic complications and provide a better understanding of the therapeutic benefits of weight loss therapy. Increased awareness of the efficacy of obesity treatments that affect body weight and the cardiometabolic complications associated with abdominal obesity will help to improve the management of obesity in clinical practice.

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