The Progression of Cardiometabolic Risk to Cardiovascular Disease

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A cluster of risk factors associated with obesity defines the metabolic syndrome and identifies cardiometabolic risk. Accumulation of fat in the visceral depot is a more reliable predictor of cardiovascular disease than is total body mass or body mass index. The recent discovery of the endocannabinoid-CB1 receptor system and its impact on the regulation of energy metabolism represents a significant advance that will help target visceral fat and its metabolic implications. As a highly active endocrine organ, visceral fat secretes many bioactive molecules, known as adipokines. Dysregulation of these adipokines contributes to the pathogenesis of the obesity-associated metabolic syndrome, resulting in insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, and vascular disease. Even modest weight reduction leads to reduced cardiometabolic risk by affecting the individual components comprising the metabolic syndrome.
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People in industrialized countries have experienced dramatic changes in their environment and lifestyles during the past 50 years. Easily and quickly available food, as well as technological advances that allow greater productivity with less effort, have resulted in major changes in energy balance. These changes have led to escalating rates of obesity, type 2 diabetes, and cardiovascular disease (CVD).[1] The combination of obesity and physical inactivity coupled with genetic predisposition results in a clustering of risk factors that now identify the metabolic syndrome: obesity, hypertension, and

an atherogenic dyslipidemia.[1] Other factors more recently appreciated include chronic inflammation and impaired fibrinolysis.[2]

Today this syndrome is reaching epidemic proportions. Extrapolation from present epidemiologic data predicts that by the year 2020, 40% of the population will be affected.[3] Obesity has been implicated as an independent causative agent of the metabolic syndrome, resulting in insulin resistance, dyslipidemia, and hypertension.[4]

Accumulation of fat in the visceral depot is a more reliable predictor of CVD than total body mass or body mass index.[5] It has been suggested that inflammation within visceral adipose cells may be a major factor in many of the abnormalities included in the metabolic syndrome and the progression to CVD.[6] The role of adipose tissue and its contribution to each component of the metabolic syndrome, and hence to CVD, is under intense investigation. The purpose of this article is to define the pathophysiology of the development of the metabolic syndrome, examine how visceral fat contributes to cardiometabolic risk, and describe how reduction in central obesity improves cardiometabolic status.

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It is now recognized that fat cells are far more than just energy depots. They are active endocrine organs and in fact represent, in total, the largest endocrine organ in the body, secreting a variety of adipocytokines that affect multiple organ systems.

Adipose Tissue and Fatty Acid Metabolism

Under most conditions, 2 major nutrients provide energy substrates: carbohydrates and fat. When carbohydrates are consumed in excess of energy needs, some of the surplus is stored as glycogen, but only in limited amounts. Some excess carbohydrate is converted to fat and subsequently stored in adipose tissue as triglycerides. These lipids enter and leave adipose tissue in the form of non-esterified fatty acids (NEFA). The release of NEFA is controlled by 2 hormones. The key enzyme is hormone-sensitive lipase (HSL), which stimulates lipolysis. A second regulator is perilipin, which prevents HSL from accessing the fat droplet. Insulin regulates lipolysis through its action on HSL.

In the postprandial state, high insulin levels result in low NEFA concentration; during fasting, NEFA levels are high. In obese individuals, however, plasma levels of NEFA are elevated in both the postprandial and fasting states. Adipose tissue in the obese, therefore, is insulin-resistant. This resistance may be explained by the adipocytes being either so large that the perilipin surrounding the fat droplet is insufficient to block HSL or so increased that each adipocyte functioning at a basal level releases more NEFA than normal.[7]

Obesity, which results in elevated NEFA levels in the circulation, also contributes to muscle insulin resistance. Approximately 70% to 80% of all glucose uptake is by skeletal muscle, which can be dependent on insulin action. NEFA entering muscle interferes with muscle glucose uptake.[8] Interference of insulin-mediated glucose uptake in muscle is a component of insulin resistance.

Obesity and the Atherogenic Dyslipidemia

High NEFA levels entering the liver increase the release of low-density lipoprotein (LDL) apolipoprotein B and very low-density lipoprotein apolipoprotein B. This increase results in elevated triglyceride levels and small, dense LDL cholesterol.[9] Obesity is also associated with increased activity of hepatic lipase, the enzyme that degrades high-density lipoprotein (HDL) cholesterol. The decrease in HDL cholesterol, together with the elevated triglyceride levels and small, dense LDL cholesterol, results in the atherogenic dyslipidemia.[10]

Visceral Fat and Adipokines

As a highly active endocrine organ, visceral fat is now known to secrete many bioactive molecules, referred to as adipokines. Some act in an autocrine or paracrine manner, whereas others are released into the circulation and have endocrine effects on other organs. Dysregulation of these adipokines contributes to the pathogenesis of the obesity-associated metabolic syndrome, resulting in insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, and vascular disease (Figure 1).[11]

Adiponectin

Adiponectin is highly expressed in adipocytes and circulates in high levels in the bloodstream. There is a strong and inverse relationship between adiponectin and both insulin resistance and inflammatory states. Adiponectin levels increase when insulin sensitivity improves after weight reduction or treatment with insulin-sensitizing drugs.

Several mechanisms for adiponectin's metabolic effects have been described. In the liver, adiponectin enhances insulin sensitivity, decreases influx of NEFA, increases fatty acid oxidation, and reduces hepatic glucose output. In muscle, adiponectin stimulates glucose use and fatty acid oxidation. Within the blood vessel wall, adiponectin inhibits monocyte adhesion, inhibits macrophage

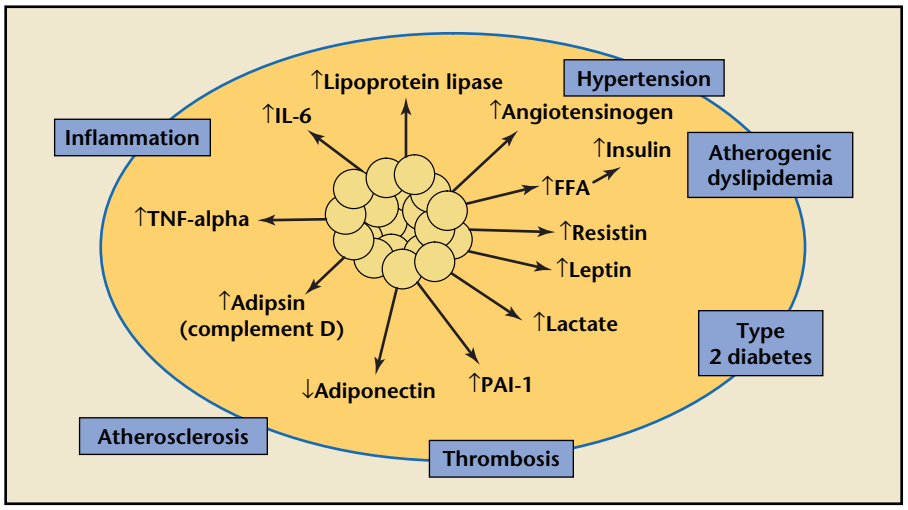

Figure 1. *Adverse cardiometabolic effects of products of adipocytes. IL, interleukin; FFA, free fatty acids; TNF, tumor necrosis factor; PAI-1, plasminogen activator inhibitor 1.*

transformation to foam cells, and decreases proliferation of migrating smooth muscle cells in response to growth factors. In addition, adiponectin increases nitric oxide production in endothelial cells. Taken together, these mechanisms suggest that adiponectin is a unique adipose-derived hormone with anti-diabetic, anti-inflammatory, and anti-atherogenic effects.[12,13]

Leptin

The discovery of leptin was the first indicator that adipose tissue was more than a storage depot.[13,14] Leptin, initially viewed as an anti-obesity hormone, appears to have a primary role in signaling an increase in appetite and decrease in energy expenditure during starvation. As fat levels increase, leptin levels increase, sending a message to the hypothalamus for satiety. Most overweight and obese individuals have elevated levels of leptin that do not suppress appetite. Leptin resistance is a fundamental pathology in obesity.[15] The mechanism of leptin resistance is unknown. Leptin has many important endocrine effects, including immune function, hematopoiesis, angiogenesis, and bone development, in addition to its effects on energy regulation, and it is the prototype for all adipose tissue–derived endocrine hormones.[13]

Inflammatory Mediators

With visceral obesity, adipose tissue secretes a number of inflammatory cytokines. These include tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, monocyte chemoattractant protein 1 (MCP-1), adipsin, and resistin.[16]

TNF-alpha. Named for causing necrosis in tumors, TNF-alpha has been shown to be identical to the cachexin secreted by macrophages.[17] TNF-alpha is also secreted by adipocytes and has been implicated in the pathogenesis of obesity and insulin resistance because it suppresses the expression of genes in adipose tissue involved in the uptake and storage of NEFA and glucose. In the liver, it suppresses genes that are involved in glucose uptake and free fatty acid (FFA) oxidation and stimulates genes responsible for synthesis of cholesterol and FFA. Levels increase with weight gain and decrease with weight loss.[17]

IL-6. This cytokine is found primarily in visceral adipose tissue. Increased levels correlate with obesity, impaired glucose tolerance, and insulin resistance. IL-6 concentration falls with weight loss. High levels predict type 2 diabetes and CVD; peripheral administration of IL-6 induces hyperlipidemia, hyperglycemia, and insulin resistance and reduces adiponectin.[18]

MCP-1. Macrophage and monocyte chemoattractant protein is associated with obesity, with increased infiltration by macrophages within adipose tissue. Activated macrophages secrete inflammatory cytokines that contribute to insulin resistance, including TNF-alpha, IL-6, and MCP-1, which is a chemokine that attracts monocytes to sites of inflammation.[13]

Adipsin. This adipose-derived complement component is one of several that are required for the enzymatic production of acylation-stimulating protein (ASP), a complement protein that affects both lipid and glucose metabolism. ASP levels correlate with adiposity, insulin resistance, dyslipidemia, and CVD.[13]

Resistin. Initial studies suggest that resistin (resistance to insulin) has a significant effect impairing insulin-stimulated glucose uptake. Studies are in progress.[13]

Coagulation and Fibrinolytic Abnormalities in Obesity

Obese individuals are at an increased risk for venous and arterial thrombotic events.[19] Obesity is associated with increased levels of fibrinogen, von Willebrand factor, factor VII, and plasminogen activator inhibitor 1 (PAI-1).[20] PAI-1 is the major inhibitor of plasminogen activation. Adipose tissue makes several substances that upregulate PAI-1.[21] The various abnormalities in coagulation and fibrinolysis that occur with obesity appear to explain the

pro-thrombotic state seen with the metabolic syndrome.[19]

Hypertension

Obesity, especially visceral obesity, is associated with hypertension in many populations. The mechanisms are multifactorial and not well understood. All components of the renin-angiotensin system, including angiotensinogen, renin, angiotensin-converting enzyme, angiotensin I, angiotensin II, and angiotensin I and II receptors, are secreted by adipose tissue, primarily visceral adipose tissue.[22] Several studies have shown that activity of the renin-angiotensin system correlates with body fat mass. These factors not only increase blood pressure but also are associated with vascular inflammation and endothelial dysfunction. Insulin resistance in the metabolic syndrome is another contributor to hypertension.

Not all organs are insulin-resistant. The compensatory hyperinsulinemia associated with muscle insulin resistance acts on the kidneys, which are normally responsive to insulin, to increase sodium reabsorption, contributing to hypertension. Dietary factors are another potential contributor. These include high sodium and fat content and low intake of potassium, fruits, and vegetables. Some people are salt-sensitive and experience an increase in blood pressure with high-salt diets. Up to one third of the population is believed to be salt-sensitive.

Adipose Tissue Depots. There is considerable heterogeneity among the various adipose depots. The subcutaneous and visceral depots have been best characterized. Visceral adipose tissue is associated with increased cardiovascular risk, including the metabolic syndrome. The anatomic location of the visceral depot may explain its endocrine function, as hormones released from this area are transported via the circulation through the hepatic portal vein to the liver, where they have direct effects. Hormones from the subcutaneous depot are secreted into the systemic circulation and have less effect on hepatic function. In addition, the visceral and subcutaneous fat depots have different adipokine expression. Relatively greater secretion of IL-6 and PAI-1 occurs in visceral adipose tissue, whereas leptin and adiponectin secretions are greater in subcutaneous adipose tissue. Adipose tissue is not a simple endocrine organ. The adipokines described and the cellular components of adipose tissue, evident by MCP-1, require extensive study before physicians will be in a position to use this information to better manage patients with the metabolic syndrome.

This background emphasizes the role that obesity, and primarily visceral obesity, plays in each component of the metabolic syndrome. It is clear that the presence of the metabolic syndrome significantly increases the risk of CVD, hence the term "cardiometabolic risk."

Decreasing CVD Events

Treatment of the metabolic syndrome consists primarily of 2 strategies: aggressive treatment of each individual risk factor and therapy directed at the root causes, including weight reduction and increased physical activity.

There are well-established data showing that cardiovascular events can be reduced by modifying risk factors, reducing blood pressure, and improving lipids. Preventing the progression to diabetes and good diabetic control also reduces events. Recommendations for treating each CVD risk factor component of the metabolic syndrome are: statins, niacin, and fibrates for lipid control; angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for blood pressure control in diabetic patients or those with insulin resistance; metformin and thiazolidinediones to improve insulin resistance; and metformin, thiazolidinediones, insulin secretagogues, and insulin to optimize diabetes management. However, it should be emphasized that weight loss alone will improve every component of the syndrome. Modest weight loss (5% to 10% of body mass) is associated with significant reduction in clinical events.[23,24] The greatest potential for successful treatment of the metabolic syndrome is reversing its root causes: overweight and obesity and physical inactivity.

In the Diabetes Prevention Program, 3234 patients with impaired fasting glucose were treated with either metformin, lifestyle modifications, or placebo.[25] The subjects treated with exercise experienced a 7% weight loss and a 58% reduction in the development of type 2 diabetes. In the Finnish Diabetic Prevention Program, 522 patients with impaired fasting glucose using diet and exercise changes experienced a 4% to 5% weight loss and a 58% reduction in the development of type 2 diabetes.[26] These 2 important studies underscore the significance of modest 4% to 7% weight losses resulting in significant reduction of the development of type 2 diabetes, which suggests concomitant reductions in future cardiovascular risks.

Loss of visceral fat in patients with abdominal obesity has shown greater beneficial effects on parameters of the metabolic syndrome than has subcutaneous fat loss in patients with subcutaneous obesity.[27] Loss of visceral fat has been shown to reduce blood pressure, lower triglyceride levels, increase HDL cholesterol

levels, and improve insulin resistance, thus modifying the cluster of risk factors and improving cardiometabolic risk.[28]

Weight Loss

The epidemic of obesity illustrates the inability of homeostatic mechanisms to offset a sedentary lifestyle and nearly unlimited access to energy-dense foods. Advising patients on dietary and lifestyle changes has been largely unsuccessful. National Cholesterol Education Program-Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III) and National Heart, Lung, and Blood Institute/American Heart Association (NHLBI-AHA) consensus reports have emphasized abdominal obesity as an important cardiovascular risk marker. Few tools exist to treat the pathophysiology in the high-risk, abdominally obese patient. Theoretically, negative calorie balance stimulated by decreased food intake and increased physical activity should result in successful weight loss, but most people who lose weight through these lifestyle changes do not maintain them over the long term, and weight is regained. People on low-calorie or popular low- to no-carbohydrate diets are often successful initially, but because long-term caloric restriction and/or removal of carbohydrates is untenable, the vast majority regains previously lost weight.

Medically supervised weight loss programs that include prudent, calorie-restricted diets guided by nutritional counseling, together with well-designed, progressive exercise and behavioral counseling, demonstrate good initial success. As with weight regain from the recidivism inherent with the low-energy or low-carbohydrate diets, sustained weight loss with well-designed medically supervised programs amounts to a scant 20%.[29] Clearly, another approach is indicated. Pharmacotherapy may be this alternative.

Limited pharmacologic therapy is available for the treatment of obesity. There are only 2 currently available medications that are approved for long-term management of obesity: sibutramine and orlistat. However, consideration of the long-term safety of sibutramine and the undesirable side effects of orlistat limits their use.

The recent discovery of the endocannabinoid-CB1 receptor system and its impact on the regulation of energy metabolism may represent an advance that could help target abdominal obesity and its metabolic implications. Rimonabant, a CB1 cannabinoid receptor antagonist, has been tested in international trials (Rimonabant in Obesity [RIO]-Lipid, RIO-Europe, and RIO-North America).[30-32] This agent may prove useful in the treatment of obesity.

Summary

The rapidly increasing incidence of obesity, along with physical inactivity and genetic predisposition, has resulted in a clustering of risk factors that define the metabolic syndrome and identify cardiometabolic risk. Obesity, especially visceral obesity, leads to abnormal FFA metabolism, insulin resistance, atherogenic dyslipidemia, and dysregulation of adipokines. Even modest weight loss, however, leads to reduced cardiometabolic risk by affecting each of the individual components comprising the metabolic syndrome. Although successful weight loss through lifestyle changes has been elusive, it is clear that regularly implemented improvements in nutrition and increased physical activity are effective initially but not over the long term. The availability of improved pharmacotherapy is a promising adjunct to lifestyle changes. ■

Main Points

- As a highly active endocrine organ, visceral fat secretes many bioactive molecules, known as adipokines. Dysregulation of these adipokines contributes to the pathogenesis of the obesity-associated metabolic syndrome, resulting in insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, and vascular disease.
- Adipose tissue secretes a number of inflammatory cytokines, including tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein 1, adipsin, and resistin, which all work to contribute to hyperlipidemia, hyperglycemia, insulin resistance, and, eventually, cardiovascular disease.
- Although weight loss alone affects all areas of the metabolic syndrome, current treatments exist for each cardiovascular disease (CVD) risk factor (statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, metformin, etc). Current pharmacologic treatments for obesity itself, however, are few and have side effects.
- Treatments aimed at the endocannabinoid-CB1 receptor system hold promise for CVD risk reduction in that they address the visceral obesity first, rather than targeting individual factors resulting from obesity.

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