

The Relation of Adipose Tissue to Cardiometabolic Risk

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Adipose tissue is an active and complex endocrine organ that secretes numerous bioactive substances, including hormones, growth factors, and cytokines. Central obesity, one of the components of metabolic syndrome, is a cardiometabolic risk factor associated with a state of chronic inflammation and coagulation, one in which the expression of certain adipocytokines, including tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and plasminogen activator inhibitor-1 (PAI-1) is more abundantly increased, while adiponectin expression is decreased. TNF- α initiates and organizes inflammatory changes in vascular tissue. IL-6, an inflammatory cytokine directly implicated in atherogenesis, exerts pleiotropic effects on a variety of tissues. An increased concentration of PAI-1, an important regulator of the endogenous fibrinolytic system, promotes continued clotting. Adiponectin, on the other hand, has potent vasculoprotective, angiogenic, anti-inflammatory, and antiatherogenic properties. Adiponectin levels are low in obese individuals and increase when weight is lost, thereby serving as a marker for cardioprotection. Weight loss has long been promoted as a means to reduce the risk of type 2 diabetes and cardiovascular disease; for example, exercise and a hypocaloric diet have been shown to decrease PAI-1 levels. Weight loss drugs, such as orlistat, a lipase inhibitor, and sibutramine, a serotonin and norepinephrine reuptake inhibitor, have both been shown to produce a decrease in C-reactive protein levels and an increase in serum adiponectin. Rimonabant, a selective cannabinoid 1 receptor antagonist in Phase III studies, also has been shown to increase adiponectin levels. These agents may play a role in the regulation of adipocytokines, which may directly affect the risk for cardiometabolic disease. (*Clinical Cornerstone*. 2006;8[Suppl 4]:S14–S23). Copyright © 2006 Excerpta Medica, Inc.

Our understanding of the relationship of obesity to cardiometabolic risk has undergone a revolution of significant clinical proportions during the last few years. Adipose tissue—an extremely diverse, complex, and multifunctional endocrine organ—is now the subject of intense scrutiny. These investigations are driven by our need to better understand the contribution of visceral fat accumulation to both *cardiovascular disease* (CVD), such as heart disease, myocardial infarction, stroke, and peripheral artery disease, and *metabolic disease*, in particular, type 2 diabetes.

According to a consensus statement recently published by the American Diabetes Association and the American Heart Association, “Obesity is a visible marker of other underlying risk factors that can be addressed.”¹ Components of metabolic syndrome—visceral

obesity, hypertension, high levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), and glucose intolerance—are a significant subset of this spectrum of risk. However, additional cardiometabolic risk factors include an inflammatory state characterized by an increase in C-reactive protein (CRP), as well as a prothrombotic state, with increases in plasminogen activator inhibitor-1 (PAI-1) and fibrinogen.² Insulin resistance has also been implicated as a possible link between visceral obesity and cardiovascular and metabolic risk factors.³ Although the exact mechanism by which fat accumulation causes impaired insulin action has not been elucidated, we know it contributes to the development of both type 2 diabetes and CVD.^{4–8}

Adipose tissue is now recognized as the hub of an intricate regulatory network that modulates many body

functions, including body weight, metabolism, inflammatory and immune status, fibrinolysis, coagulation, angiogenesis, and reproduction, among others.^{9,10} The body's largest energy reservoir, white adipose tissue (WAT) is composed of adipocytes (fat cells), which are the most numerous cell type; stromovascular cells; a connective tissue matrix; nerve tissue; and immune cells.^{11,12} Adipocytes can vary widely in size (20–200 μm in diameter) and are sites for storing and releasing energy.¹³ They warehouse energy as triglycerides during periods of caloric excess and release free fatty acids (FFAs) and glycerol when energy expenditure is required (Figure 1).¹⁴ Adipocytes expand greatly in volume to accommodate excess triglycerides, with adipose tissue depots having an almost unlimited capacity for growth.¹⁵ Present in the stromovascular matrix of adipose tissue are preadipocytes, which are distinguished by their ability to differentiate into various cell types,^{11,16} and macrophages, which tend to accumulate in high numbers in excess adipose depots.¹¹

All 3 cell types (ie, adipocytes, preadipocytes, and macrophages) can undergo changes that implicate them in the processes of inflammation and metabolic dysfunction. Although adipose tissue and its constituent cells and secretory products are important regulators of energy homeostasis, this paper reviews the consequences of adipose tissue dysfunction from the perspective of adipose tissue–secreted proteins involved in inflammation, atherosclerosis, and cardiometabolic risk.

ADIPOCYTE SECRETORY PRODUCTS INVOLVED IN INFLAMMATION AND ATHEROSCLEROSIS

Adipocytes secrete various bioactive proteins, collectively called *adipokines* or *adipocytokines*.^{9,12,17–21} Through their secretory products, the cells within adipose tissue depots acquire an ability to cross-talk with each other and with other organs such as brain, liver, and muscle.¹⁶ Adipocytokines, therefore, can exert local, peripheral, and central

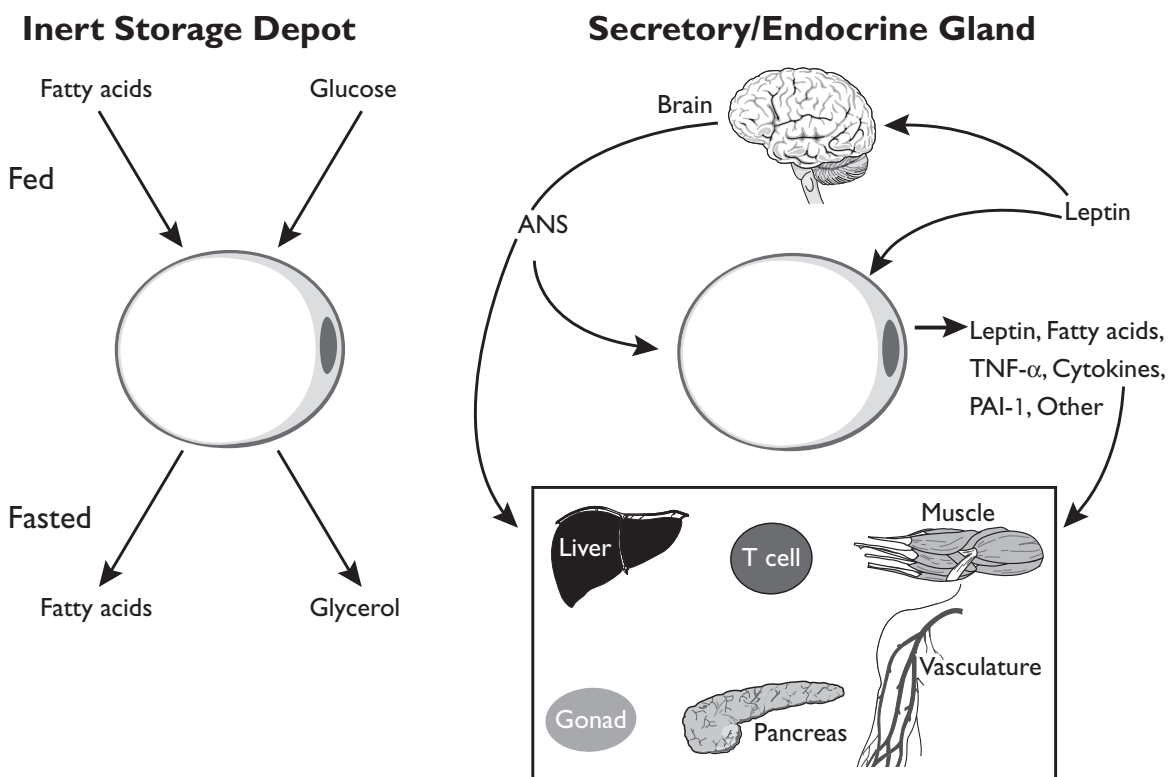


Figure 1. Evolving view of the biological functions of the adipocyte. Previously, adipocytes were considered to be inert storage depots releasing fuel as fatty acids and glycerol in time of fasting or starvation. More recently, it has become clear that adipocytes are endocrine glands that secrete important hormones, cytokines, vasoactive substances, and other peptides. ANS = autonomic nervous system; TNF-α = tumor necrosis factor-alpha; PAI-1 = plasminogen activator inhibitor-1. Adapted with permission.¹⁴

KEY POINT

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effects (Table).^{11,15} Some of these bioactive proteins—for example, cytokines such as PAI-1, tumor necrosis factor- α (TNF- α), and interleukin (IL)-6—contribute to a state of chronic systemic and local vascular inflammation and enhanced coagulation as the volume of adipose tissue expands.^{11,21,22} Other bioactive proteins, such as adiponectin, favorably affect the inflammatory milieu.²² Some factors work in opposition to each other, while others work in parallel. For example, as adipose tissue expands, the concentration of PAI-1 increases,²³ working in parallel, while the concentration of adiponectin decreases,^{24,25} working in opposition. Circulating levels of TNF- α and IL-6 are implicated in endothelial dysfunction and vascular inflammation in addition to having metabolic effects on insulin desensitization.¹¹

Many theories have been proposed to explain the relationships between visceral adiposity, inflammation, and

atherosclerosis. The complications of obesity—in particular, CVD and diabetes—are hypothesized to be due in part to a state of chronic, low-grade, subclinical inflammation.^{26,27} Visceral adiposity is theorized to promote “inflammatory tone” by way of activated adipocytes and macrophages that infiltrate adipose tissue in high numbers during weight gain.²⁷ In lean individuals, small adipocytes are generally considered to be insulin-sensitive, functioning to maintain metabolic homeostasis.^{14,28} In obese individuals, however, enlarged, activated adipocytes recruit macrophages and release various factors that promote both inflammation and insulin resistance (Figure 2).^{15,22,28} Macrophage recruitment—whether by adipocytes or from the bone marrow in response to monocyte chemoattractant protein-1 (MCP-1) stimulation by preadipocytes and endothelial cells—appears to be a mechanism that contributes to local and systemic inflammation.²⁷ Both adipocytes and macrophages are capable of subsequently releasing inflammatory factors,²⁷ although adipocytes appear to have a

TABLE. KEY CONCEPTS IN THE RELATION BETWEEN ADIPOSE TISSUE AND INFLAMMATION.

Cells

- Macrophages are a normal component of adipose tissue.
- Obesity is associated with increased numbers of macrophages in adipose tissue.
- Obesity is associated with the presence of activated macrophages in adipose tissue.
- There is cross-talk between adipocytes and lymphocytes in lymph nodes.

Molecules

- Adipocytes produce many factors modulating immunity and inflammation.
- Leptin exerts mostly proinflammatory and immune-potentiating effects.
- Adiponectin exerts mostly anti-inflammatory effects.

Diseases

- Low adiponectin levels in type 2 diabetes are a possible link to insulin resistance.
- Several conditions are associated with altered adipocytokine levels, but the significance of this observation is unclear.

Adapted with permission.¹¹

greater proinflammatory potential.¹⁵ Both endothelial dysfunction and insulin resistance have been found to contribute to atherosclerosis.²²

The extent to which adipose tissue actually generates systemic or localized inflammation is still a matter of intense research, as the precise contribution of adipose tissue to circulating levels of inflammatory cytokines and other bioactive factors is not known.^{15,26} There is evidence that elevation of inflammatory cytokines and acute-phase proteins produced by adipose tissue in obese individuals represents a localized phenomenon in expanding fat deposits; these resulting elevations may accompany tissue hypoxia and angiogenesis in the expanding deposits.²⁶ Adipocytes are connected to the vascular network,^{23,29} and adipocytokines freely enter the systemic circulation.²³ Similarly, abnormal levels of adipocyte-derived factors are known to be implicated in derangements of cardiovascular physiology, vascular homeostasis, and inflammation through their direct and indirect effects on blood vessels that express receptors for many of these factors.⁹

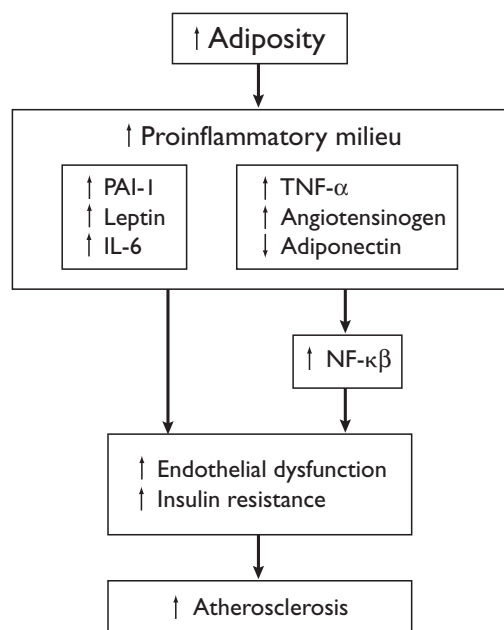


Figure 2. Many of the adipocytokines whose expressions are altered during obesity promote inflammation and can promote insulin resistance, endothelial dysfunction, and, ultimately, atherosclerosis. PAI-1 = plasminogen activator inhibitor-1; IL-6 = interleukin-6; TNF- α = tumor necrosis factor-alpha; NF- κ B = transcription factor nuclear factor- κ B. Adapted with permission.²²

KEY POINT

Both endothelial dysfunction and insulin resistance have been found to contribute to atherosclerosis.

Adiponectin

Adiponectin, the most abundantly secreted adipocytokine from differentiated adipocytes, has vasculoprotective, angiogenic, anti-inflammatory, and antiatherogenic properties (**Figure 3**).^{30,31} High adiponectin levels are associated with a reduced risk of myocardial infarction in men,²³ while low serum adiponectin levels are reported in obese individuals and in those with hypertension, coronary artery disease, and type 2 diabetes.^{23,31} In an *in vitro* study of human aortic endothelial cells, adiponectin reduced the attachment of monocytes to vascular endothelial cells, an early event in atherosclerotic vascular change.³² In ischemia-reperfusion injury and hypertrophic cardiomyopathy, adiponectin protects the myocardium against vascular damage through 2 important, independent mechanisms: stimulation of 5'-adenosine monophosphate-activated protein kinase (AMPK) and activation of cyclo-oxygenase-2 (COX-2).^{30,33} After cardiac damage, AMPK stimulation inhibits apoptosis in myocytes and fibroblasts and suppresses cardiac myocyte hypertrophy, that is, it inhibits hypertrophic remodeling.³⁰ COX-2 activation mediates anti-inflammatory effects in cardiac cells.³⁰ Future studies are expected to characterize more precisely the influence of adiponectin on apoptosis, inflammation, and hypertrophy in cases of established heart failure in which paradoxical low levels of adiponectin offer cardioprotection.³⁰ The exact role of adiponectin in metabolism and inflammation is complicated by the variation in its 3 circulating forms: a hexamer, a trimer, and a low-molecular-weight molecule.³¹

Adiponectin also has insulin-sensitizing effects. Hotta et al³⁴ found that adiponectin levels are inversely related to fasting plasma insulin and glucose levels. Plasma concentrations of adiponectin were observed to be significantly lower in obese persons than in those of normal body weight.²⁴ Additionally, weight loss in obese individuals leads to increased adiponectin levels, whereas

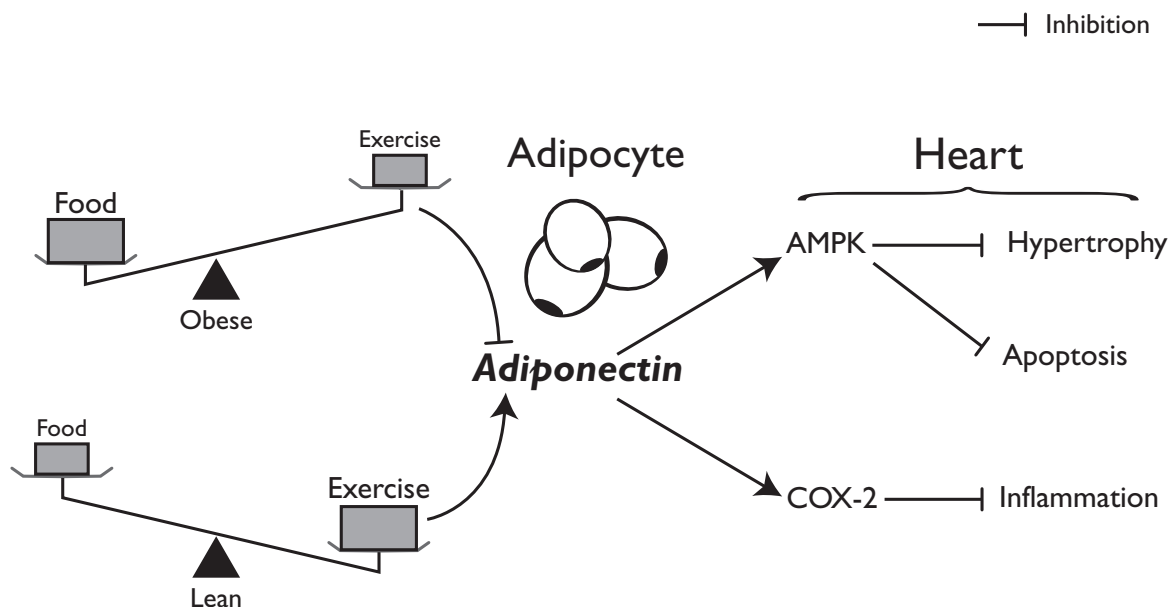


Figure 3. Cardioprotective actions of adiponectin. The plasma adiponectin level is negatively regulated by adiposity, which is influenced by levels of food intake and physical activity. Adiponectin stimulates myocardial adenosine monophosphate-activated protein kinase (AMPK) signaling, leading to a suppression of myocyte hypertrophy and apoptosis. Adiponectin also stimulates cyclo-oxygenase-2 (COX-2) expression, resulting in a reduction in cardiac inflammation. Adapted with permission.³⁰

weight gain, and particularly an increase in visceral fat, is linked to a decrease in adiponectin levels.³⁵

A lower adiponectin level may increase the risk of atherosclerosis; therefore, adiponectin could be an indicator of diabetes-associated macroangiopathy. Because a reduction in body fat results in an increase in adiponectin, efforts to reduce body fat in an effort to normalize plasma adiponectin levels may be important in preventing the development of atherosclerosis, a hypothesis that requires confirmation with prospective studies.

KEY POINT

Weight loss in obese individuals leads to increased adiponectin levels, whereas weight gain, and particularly an increase in visceral fat, is linked to a decrease in adiponectin levels.

Leptin—A Metabolic Hormone and Proinflammatory Cytokine

Discussions about adipose tissue generally begin with a summary about leptin, the most intensively researched adipocytokine since its discovery in 1994. Leptin levels increase as adipose tissue mass increases, and it is well established as an important metabolic regulator of appetite and satiety.^{36,37} However, leptin also has less well-understood effects on inflammatory and immune responses through its pleiotropic effects on T lymphocytes, monocytes, and endothelial cells.¹¹ In obese individuals, leptin is reported to upregulate adhesion molecules on endothelial cells, which leads to monocyte transmigration, higher numbers of WAT-resident macrophages, and correspondingly higher levels of TNF- α , IL-6, and other cytokines.¹¹ Leptin also functions as a proinflammatory cytokine in a number of autoimmune inflammatory conditions.^{36,37} Although leptin levels are increased in response to secretion of acute-phase adipocyte-derived cytokines such as TNF- α and IL-6, details of many of these interrelationships are still unknown.^{36,37}

Plasminogen Activator Inhibitor-1

PAI-1, which inhibits tissue plasminogen activator, is a regulator of the endogenous fibrinolytic system.³⁸ Increased concentrations of PAI-1 retard the clearance of clots and promote the development of thrombi, which can potentiate myocardial infarction and stroke.⁹ PAI-1 appears to exert a systemic effect in atherosclerosis and local effects in adipose tissue.¹⁶ Overexpression of PAI-1 in adipose tissue has been reported in obese mice and obese individuals,^{16,39} and elevated PAI-1 concentrations have been detected in the plasma of obese individuals.^{16,23} A close association between enhanced PAI-1 expression and intra-abdominal tissue distribution also has been reported.¹⁹

Tumor Necrosis Factor- α

Adipocytes are both the source and the target of TNF- α ,⁹ a multifunctional regulatory cytokine that is implicated in chronic inflammation contributing to atherosclerosis, the production of additional inflammatory cytokines, and induction of insulin resistance.^{9,10,22} TNF- α activates transcription factor nuclear factor- κ B, which initiates and organizes inflammatory changes in vascular tissue.^{22,40} These vascular inflammatory changes produce endothelial dysfunction through expression of adhesion molecules on endothelial cells and vascular smooth muscle cells.²² In addition, increased TNF- α secretion from visceral fat appears to be a strong inhibitor of adiponectin promoter activity, which may partially explain the negative relationship between visceral adiposity and adiponectin levels.²³

In addition to its proinflammatory effects, TNF- α has been considered an important link to obesity and insulin resistance.^{9–11} Local elevations of TNF- α directly interfere with insulin signaling, which ultimately leads to insulin resistance.^{14,15} TNF- α expression and production are also increased in the adipocytes of obese individuals.^{11,14,15} In fact, levels of TNF- α mRNA are reported to be positively correlated with body fat.⁹ TNF- α signaling is mediated by 2 receptor subtypes (type I and type II), both of which are expressed in adipocytes, the main source of TNF- α .¹⁰

Interleukin-6

IL-6, a stress-induced, inflammatory cytokine directly implicated in atherogenesis,²² exerts pleiotropic effects on a variety of tissues.⁹ Approximately 30% of circulating IL-6 is from WAT,⁴⁰ with visceral WAT producing higher levels of IL-6 than subcutaneous WAT.¹¹ Adipocytes and

macrophages both contribute to WAT-derived IL-6, although the ultimate stimulus for IL-6 production in the presence of excess adiposity is currently unknown.

Increased serum IL-6 is predictive of future cardiovascular problems.¹⁰ High levels of IL-6 are thought to be responsible for the increase in acute-phase proteins seen in obese patients, in particular, CRP, which is an important marker of vascular inflammation.^{11,22} This mechanism of inflammation has been proposed as tantamount to low-density lipoprotein cholesterol in its contribution to atherosclerosis.²² Similarly, in 1 study, IL-6 was significantly associated with body mass index, waist circumference, and visceral adiposity in obese subjects.⁴⁰ IL-6 tends to have a broad range of systemic effects on peripheral tissues such as muscle and liver, in addition to its effects on the endothelium.²⁷

Other Cytokines

Numerous other cytokines and chemokines are expressed by WAT, including IL-8, IL-10, MCP-1, and macrophage inflammatory protein 1, although much less is known about their synthesis, release, and effects.

THE ASSOCIATION OF ADIPOSE TISSUE TO CARDIOMETABOLIC RISK

It is important to understand the elevated production of inflammation-related and thrombosis-related adipocytokines in the development of diseases linked to obesity, particularly type 2 diabetes and CVD. Adipose tissue is involved in extensive cross-talk with other organs and multiple metabolic systems through changes in adipocytokine levels in the circulation as adipose tissue expands.²¹ A result can be the organ damage that is a hallmark of these diseases.

Adipose tissue that accumulates in the abdominal area tends to be associated with CVD. Fat that collects in this area adversely affects insulin action and glucose disposal; it is thought that this occurs partly through an increase in the release of FFAs, which travel to the liver and are released into the systemic circulation. The mechanism by which this occurs may relate to increased lipolysis, leading the liver to increase production of glucose and the skeletal muscle to decrease glucose uptake. The liver also increases production of very-low-density lipoprotein, which results in a fatty liver. In addition, fat accumulates in skeletal muscle. The net result is an increase in blood glucose, blood pressure, triglycerides, small dense low-

density lipoprotein particles, and inflammatory markers, as well as a decrease in HDL-C.⁴¹ In a study by Pouliot et al,⁴² obese men and lean controls were compared with respect to risk factors for CVD. The obese men with high visceral fat accumulation had a greater degree of glucose intolerance, increased insulin resistance, and higher triglyceride levels. They also had lower HDL-C levels than the controls.

Reducing Obesity to Manage Cardiometabolic Risk

Both lifestyle modification and drug therapy are helpful in reducing obesity to manage cardiovascular and metabolic risk factors.

Lifestyle Modification

Lifestyle modification can reduce cardiovascular risk factors. The National Cholesterol Education Program Adult Treatment Panel III recommends a combination of diet and exercise in place of drug treatment for patients who are in an intermediate range of coronary heart disease risk.⁴³ Lifestyle modification can also affect the cytokines secreted by adipose tissue. For example, in the Finnish Diabetes Prevention Study,⁴⁴ patients with impaired glucose tolerance were randomized to a control group or an intervention group. The intervention group followed an intensive program aimed at weight reduction, healthy diet, and increased physical activity. During the first year, PAI-1 levels decreased 31% in the intervention group but showed no change in the control group ($P < 0.001$). Changes in PAI-1 persisted throughout the 3-year follow-up. The investigators concluded that reduction in fat stores was the most important factor in long-term effects on fibrinolysis, as indicated by the reduced PAI-1 levels.

Drug Therapy

Two weight loss drugs are currently available, orlistat and sibutramine. Orlistat is indicated for obesity management, including weight loss and maintenance, when used in conjunction with a reduced-calorie diet. Orlistat inhibits the action of lipases, enzymes that break down dietary fat in the gastrointestinal tract, and thereby prevents some dietary fat from being digested. Sibutramine acts centrally by inhibiting serotonin and norepinephrine reuptake from neuronal synapses and is effective in promoting and maintaining weight loss in obese patients.⁴⁵ In a 6-month study,⁴⁶ obese nondiabetic women were given either sibutramine or orli-

stat to determine the effects of these agents on serum adipocytokines. Although both regimens resulted in weight loss and a decrease in waist circumference, the weight loss seen with sibutramine was greater than that seen with orlistat (5.4% vs 2.5%). Both sibutramine and orlistat produced a decrease in CRP levels and an increase in serum adiponectin.

Rimonabant, a selective cannabinoid type 1 (CB₁) receptor antagonist, is currently in Phase III development. Activation of neuronal CB₁ receptors by endogenous cannabinoids, such as anandamide, has been shown to increase appetite in animal models.⁴⁷ Rimonabant blocks these cannabinoids and thereby effects a decrease in appetite. In addition to the central effects on feeding behavior, preclinical studies with rimonabant demonstrated peripheral effects (eg, modulation of hepatic lipogenesis, glucose homeostasis, and adipose tissue metabolism). For example, rimonabant was shown to increase adiponectin gene expression and production in adipose tissue,⁴⁸ increase insulin-mediated glucose uptake in isolated skeletal muscle,⁴⁹ and decrease hepatic fatty acid synthesis and lipid accumulation after ingestion of high-fat foods.⁵⁰

Three randomized, double-blind, placebo-controlled, Phase III clinical trials have investigated the effects of rimonabant in overweight or obese patients with either hypertension or dyslipidemia.^{51–53} In the Rimonabant in Obesity (RIO)–North America study, rimonabant plus standard dietary intervention effected significant reductions in body weight and waist circumference and produced favorable changes in HDL-C, triglyceride, fasting insulin, and HOMA-IR (homeostasis model assessment of insulin resistance) levels that were approximately twice those expected from achieved weight loss alone.⁵¹

KEY POINT

Rimonabant, plus standard dietary intervention, effected significant reductions in body weight and waist circumference and produced favorable changes in HDL-C, triglyceride, fasting insulin, and HOMA-IR levels.

Patients who received rimonabant 20 mg for 2 years maintained both the weight loss and the differences in cardiometabolic risk factors compared with patients receiving placebo. Similar 1-year findings were reported in the RIO–Europe study.⁵² A third study, RIO–Lipids, enrolled obese or overweight patients with untreated dyslipidemia.⁵³ Rimonabant 20 mg produced significant and sustained reductions in waist circumference and body weight. This treatment also produced significant improvements in plasma triglyceride and HDL-C levels; the ratio of total cholesterol to HDL-C; low-density lipoprotein particle size; adiponectin, insulin, and plasma CRP levels; glucose tolerance; and the proportion of patients with metabolic syndrome.

CONCLUSIONS

Obesity produces widespread dysregulation of adipocyte number, size, function, and distribution, which, in turn, initiates profound metabolic and inflammatory disturbances. Visceral fat accumulation is characterized by the presence of activated adipocytes and macrophage infiltration, cells whose secretory factors contribute to local, peripheral, and central proinflammatory effects. Many of these factors are released in proportion to the amount of visceral fat. Adipocytokines, such as TNF- α , IL-6, and PAI-1, which are involved in the processes of vascular inflammation, thrombosis, and coagulation, and those in opposition, such as adiponectin, determine the balance of the proinflammatory milieu, a contributing factor in the progression of insulin resistance, endothelial dysfunction, and atherosclerosis. Future investigations are likely to uncover specific differences in the secretory behavior of specific adipose tissue depots. Study results suggest that the antiobesity effect of weight reduction with lifestyle modification, drug therapy, or both may go beyond weight change to changes in adipocytokines that directly affect the risk of type 2 diabetes and CVD.

KEY POINT

The antiobesity effect of weight reduction with lifestyle modification, drug therapy, or both may go beyond weight change to changes in adipocytokines that directly affect the risk of type 2 diabetes and CVD.

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