Endocrine and Metabolic Effects of Fat: Cardiovascular Implications

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ABSTRACT

The prevalence of obesity is increasing rapidly in both industrialized and developing nations. Obesity causes complex metabolic, endocrine, and hemodynamic changes that may lead to adverse cardiovascular outcomes such as coronary heart disease and congestive heart failure. Adipose tissue is no longer considered to be an inert organ of energy storage, but in fact possesses important endocrine and metabolic functions that are closely involved in energy homeostasis. During the past decade, our understanding of the unique pathophysiologic changes that occur with obesity has rapidly grown. This review discusses our current understanding of the endocrine and metabolic effects of fat and their potential relation to cardiovascular disease.

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The prevalence of obesity is rapidly increasing worldwide, in both industrialized and developing nations. Often described as a modern-day epidemic, obesity represents a common preventable cause of death in the United States. According to the most recent United States Census report, more than 60% of Americans are either overweight or obese. The increase in the prevalence of overweight and obesity has occurred in both men and women, in all age groups, and in all ethnic groups.

Obesity, particularly central obesity, may be considered a state of low-grade inflammation that leads to an increased risk for cardiovascular disease through various pathophysiologic processes discussed herein. Adipose tissue is no longer considered an inert organ for energy storage, but rather an extremely active organ that helps mediate energy homeostasis and whose activity is delicately regulated by a complex network of autocrine, paracrine, and neuroendocrine signals.

ROLE OF THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system is activated in obesity despite an increase in intravascular volume and sodium retention. There are at least 3 mechanisms of renin-angiotensin system activation in obesity: secretion of angiotensinogen from adipose tissue resulting in increased activation of the local and systemic renin-angiotensin system; the action of an adipocyte-derived factor that enhances the release of a hepatic stimulator of aldosterone synthesis; and increased circulating renin levels, which might stimulate increased sympathetic nervous system activity.

Local and systemic renin-angiotensin system up-regulation and angiotensin II promote cardiac hypertrophy, vascular hyperplasia, endothelial dysfunction, increased tissue reactive oxygen species, and cardiac fibrosis. Renin-angiotensin system up-regulation also stimulates coagulation and platelet aggregation through its effect on plasminogen activator inhibitor-1 (PAI-1) and thus creates a prothrombotic environment. With renin-angiotensin system up-regulation, the balance that exists between tissue inhibitor of metalloproteinase and matrix metalloproteinase is altered, resulting in increased extracellular matrix and perivascular remodeling fibrosis. Local renin-angiotensin system up-regulation in adipose tissue causes hypertension to worsen by activating angiotensin I receptors present in adipose tissue. Conversely, renin-angiotensin system blockade has the beneficial effect of improving hypertension.

Elevated serum aldosterone levels due to unregulated renin-angiotensin system activity predispose to hypertension, electrolyte abnormalities such as hypokalemia and hypomag-
nerves, activation of PAI-1, and increased levels of reactive oxygen species. They also promote a proinflammatory environment. These alterations may increase the risk for developing left ventricular hypertrophy, accelerated atherosclerosis, acute coronary syndromes, cardiac arrhythmias, and cardiac fibrosis. This notion is supported by data from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and Randomized aldactone Evaluation Study (RALES) trials, which demonstrated that aldosterone antagonists reduced left ventricular diastolic dysfunction, improved vascular compliance, and decreased the risk for sudden cardiac death. Weight loss was associated with decreased plasma renin activity and serum aldosterone levels in a study of obese patients randomized to a low and medium salt, weight-reduction diet for 12 weeks.11

ROLE OF THE SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system and parasympathetic nervous system comprise the autonomic nervous system. This system, along with the endocrine system, is responsible for maintenance of homeostasis. The adrenal medulla and sympathetic nervous system form the sympathoadrenal system. The adrenal system exerts its action through epinephrine secreted from the adrenal medulla, whereas the sympathetic nervous system acts by secretion of norepinephrine from sympathetic nerve endings. The stress centers of the sympathetic nervous system and parasympathetic nervous system comprise the tightly interconnected central autonomic nervous system and are usually activated simultaneously.

Some animal studies have shown decreased sympathetic nervous system activity with development of obesity. However, more recent studies in human obesity do not support these observations. In humans, the daily energy expenditure is characterized by the resting metabolic rate, the thermic effect of the food, and the energy cost of physical activity. The contribution of the sympathetic nervous system to the daily energy expenditure, however, is small (~5%) in normal subjects consuming a weight-maintenance diet. Thus, it is still not clear whether under-activity of the sympathetic nervous system led to obesity in animal studies or was just a consequence. Based on our current understanding, it is appropriate to say that low sympathetic nervous system activity may be involved in the pathogenesis of obesity in genetically susceptible populations. In fact, most studies assessing sympathetic nervous system activity in obese and lean subjects indicate that obesity is associated with enhanced sympathetic nervous system activity.

Heightened sympathetic nervous system activity has been implicated in the increased risk of cardiovascular disease and hypertension in obesity. Increased sympathetic tone is thought to contribute to the obesity-hypertension syndrome. Obese hypertensives are more likely to have increased sympathetic tone than lean hypertensives. Weight loss reduces both sympathetic tone and blood pressure in obese hypertensives. Centrally active alpha-2 adrenergic blockers blunt the hypertensive response in dogs fed a high-calorie diet. Increased renal sympathetic nerve activity may also contribute to obesity hypertension by stimulating the renin-angiotensin system.

In addition to stimulation by the central nervous system and renin angiotensin system, several other mechanisms and mediators have been proposed to explain the genesis of adrenergic overactivity noted in the obese. Hyperinsulinemia, elevated free fatty acids and leptin, and impaired cardiopulmonary and altered arterial baroreflex sensitivity have been proposed as contributing factors to adrenergic overactivity in this population.

Activation of the sympathetic nervous system in obesity contributes to a number of adverse cardiovascular effects in addition to hypertension. These include cardiac hypertrophy, vascular smooth muscle hypertrophy, arterial remodeling, and endothelial dysfunction.

ROLE OF INSULIN RESISTANCE AND HYPERINSULINEMIA

Obesity is strongly associated with insulin resistance, hyperinsulinemia, and the cardiometabolic syndrome. Insulin resistance may result from prereceptor, receptor, or postreceptor abnormalities. Prereceptor causes include anti-insulin antibodies and abnormal (mutated) insulin. Receptor causes include decreased number of receptors, insulin receptor structural modifications, and insulin receptor blocking antibodies. Postreceptor mechanisms involve the postreceptor signaling pathway. The mechanism of insulin resistance in obesity is due to postreceptor mechanisms. Insulin resistance results in impaired biological and physiological response to insulin in tissue. The action of insulin is mediated through the tyrosine kinase receptor.

The physiological action of insulin can be divided into acute effects and chronic effects. Acute effects include those that regulate intermediary metabolism, and chronic effects include the growth and proliferative effects of insulin.
These 2 different actions are possible because of activation of 2 different cascades of action by insulin. One pathway transmits the insulin signal through insulin receptor substrate proteins and phosphatidylinositol 3-kinases to a series of intracellular proteins. Activation of this pathway is crucial for transducing the actions of insulin-like growth factor 1 in cardiovascular tissue as well as conventional insulin-sensitive tissues. Phosphotidylinositol-kinase mediates the increases in nitric oxide, sodium pump and potassium channel activity, and calcium myofilament sensitivity by increasing the trafficking and translocation of nitric oxide synthase and cation pump units as well as glucose transporters. The alternate action of insulin proceeds through Grb2/Sos and ras, leading to activation of the mitogen-activation protein kinase isoforms ERK1 and ERK2. Activation of the mitogen-activation protein kinase pathway results in cell growth and extracellular matrix expansion. In obesity and diabetes mellitus, this resistance to insulin’s action is mainly due to the metabolic and not the trophic action of insulin. Insulin resistance and the compensatory hyperinsulinemia noted in these individuals may contribute to the development of obesity cardiomyopathy. Also, insulin resistance is not uniform in all tissue, and this causes increased activity of insulin in certain tissue and an attenuated response in others. Within cells, insulin resistance may exacerbate certain actions of insulin and inhibit others.

Insulin resistance and hyperglycemia associated with obesity may result in cardiac changes similar to those described in diabetic cardiomyopathy. Hyperglycemia is thought to cause myocardial dysfunction and mediate tissue injury through formation of reactive oxygen species. Increased availability of glucose due to insulin resistance results in increased glucose autooxidation and, consequently, increased mitochondrial generation of superoxide. The generation of reactive oxygen species in the milieu of hyperglycemia results in a series of secondary independent biochemical pathways that have been implicated in the pathogenesis of hyperglycemia-induced myocardial structural and functional changes. Some of the structural changes seen are increased ventricular wall stiffness and impaired ventricular filling. Insulin resistance also sets in motion a cascade of biochemical changes in endothelial cells, macrophages, and vascular smooth muscle cells, which result in the secondary over-expression of proinflammatory cytokines, adhesion molecules, and chemokines, as well as increased production of reactive oxygen species and activation of nuclear factor kappa B. Lastly, the other biochemical pathway that is activated in hyperglycemia is protein kinase C, which becomes a trigger for cardiac hypertrophy, increased extracellular matrix, and decreased sarco(endoplasmic reticulum Ca2+-ATPase activity. The above phenomena contribute to cardiac remodeling fibrosis and diastolic dysfunction in diabetes mellitus. Yet another possible mechanism of cardiac hypertrophy in chronic hyperinsulinemia is through augmented phosphatidylinositol 3-kinases Akt-1 activation via sympathetic nervous system activation.

### ROLE OF FREE FATTY ACIDS

Obesity is associated with increased fasting and postprandial concentrations of free fatty acids and triglyceride. This results in distribution of free fatty acids to nonadipose tissue such as skeletal muscle and myocardium, potentially resulting in lipotoxicity. In obese individuals, cardiomyocytes derive free fatty acids directly from the surrounding epicardial fat and from the circulating blood carrying free fatty acids from other visceral fatty deposits. Accumulation of lipid in cardiac muscle may lead to clinical manifestations of cardiac dysfunction, as evidenced by the increased incidence of heart failure in obese individuals. These cardiac changes in obesity may progress over time to produce left ventricular diastolic and systolic dysfunction. High free fatty acid levels also are thought to contribute to hypertension by increasing sympathetic activity, enhancing sympathetic vascular responses, and by impairment of endothelium-dependent vasodilatation.

### ROLE OF LEPTIN

Leptin, a peptide synthesized and secreted by adipocytes, has gained much attention as a mediator of obesity. It is mainly involved in the regulation of appetite, energy metabolism, and body weight. Leptin interacts with leptin receptors in numerous hypothalamic nuclei, including the ventromedial hypothalamus, which is the satiety center. Binding of leptin to the appropriate leptin receptor triggers intracellular signaling processes in the ventromedial hypothalamus, which in turn signals the brain that adequate food has been ingested. Decreased leptin levels or leptin resistance can result in loss of satiety and weight gain. Primary leptin deficiency, as observed in the ob/ob mouse, is not common among obese humans. On the contrary, circulating levels of leptin are typically high in these individuals.

Leptin resistance is often accompanied by diabetes mellitus and the cardiometabolic syndrome, and it frequently coexists with insulin resistance. Recent studies indicate that leptin receptors (Ob-R) have a widespread tissue distribution including liver, kidney, lungs, pancreas, and heart. Also, some of the leptin binding sites in the brain are related to regions that control the cardiovascular system. In fact, animal studies have shown a relationship between cardiac hypertrophy and disruption of leptin signaling. In one study, leptin deficiency in ob/ob mice led to cardiac dysfunction, which was reduced when exogenous administration of leptin was carried out. This suggests that the leptin receptor in the myocardium may have a role in cardiac remodeling in these models of obesity. Similarly, leptin receptors are present on other cell types that may affect the vascular disease processes, including white blood cells, platelets, endothelial cells, and vascular smooth muscle cells. The presence of leptin receptors in these cell types may be an important key linking the role of leptin in the promotion of angiogenesis, thrombosis, atherosclerosis, and neointimal hyperplasia that has been demonstrated in various animal models. The physiological role of leptin is
complex, and leptin could be a key link between obesity and the development of cardiovascular disease. This might be mediated through its effects on blood pressure, platelet aggregation, arterial thrombosis, and the subsequent inflammatory vascular response and ventricular hypertrophy. Another important concept is the presence of selective leptin resistance. Obese humans continue to overeat despite elevated circulating leptin levels, indicating a failure of feedback mechanisms on satiety. Yet, they retain intact feedback in the sympathetic nervous system, as evidenced by development of hypertension. The hypothesis of selective leptin resistance, however, has been tested only in rodents and not in humans.

**PROINFLAMMATORY AND PROTHROMBOTIC CHANGES**

Obesity is sometimes referred to as a low-grade inflammatory condition because adipose tissue in general and visceral adipose tissue in particular are rich in inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, C-reactive protein (CRP), and PAI-1. These cytokines, in turn, are considered major regulators in the production of acute-phase reactants such as CRP, PAI-1, and fibrinogen by the liver. Elevated CRP levels confer an increased risk for cardiovascular disease, and it is possible that the relationship between obesity and vascular disease might depend, in part, on the increased production and release of inflammatory mediators from adipose tissue. However, a direct cause-effect relationship has not been clearly established. Further, it has been proposed that the secretion of interleukin-6 by adipose tissue, combined with the actions of adipose tissue-expressed tumor necrosis factor-alpha in obesity, could explain the association of insulin resistance with inflammation, endothelial dysfunction, coagulopathy, and cardiovascular disease.

The increased risk of cardiovascular disease in obesity is partly explained by disturbances of hemostatic and fibrinolytic systems. Adipokines secreted from adipose tissue can modify vascular responses and anti fibrinolytics (particularly PAI-1), a milieu that favors fibrin accumulation and coagulation. Elevated plasma levels of PAI-1 produced by omental adipocytes are strongly associated with the degree of insulin resistance and could be an underlying mechanism for the thrombotic tendency and the progression of atherosclerosis associated with obesity.

The relation of PAI-1 to weight gain suggests that it may behave as a potential therapeutic target for controlling cardiovascular disease morbidity in obese subjects. Obesity is characterized by higher plasma concentrations of antithrombotic factors, such as tissue-type plasminogen activator and protein C, compared with lean controls. The increase in plasma levels of these factors may represent a protective response to counteract the expected increased prothrombotic factors. Finally, some hormonal abnormalities (androgen, increased catecholamine levels) associated with the accumulation of body fat may contribute to the impairment of the coagulation pathway in obesity. The prothrombotic changes associated with obesity are present in both males and postmenopausal females, suggesting possible loss of naturally endowed cardiovascular protection that females possess.

**ADIPOKINES ASSOCIATED WITH OBESITY**

There are numerous cytokine hormones secreted by adipose tissue that play an important role in the regulation of energy homeostasis, insulin action, and lipid metabolism. A detailed description of the various adipokines secreted in adipose tissue is beyond the scope of this review, but some merit attention, including adiponectin, acylation-stimulating protein, apelin, and visfatin.

Acylation-stimulating protein is a lipogenic adipocytokine whose precursors, complement (C3, adipin, and factor B) are synthesized and secreted by adipose tissue in a differentiation-dependent manner. Acylation-stimulating protein is linked to the pathogenesis of obesity via its action to enhance triglyceride synthesis and storage in the adipocyte. Elevated levels of this adipocytokine are observed with obesity, diabetes mellitus, and insulin resistance. Mice with a genetic knockout of C3 are unable to produce acylation-stimulating protein and do not develop diet-induced obesity or insulin resistance.

Adiponectin is yet another adipokine that is secreted from adipose tissue. Adiponectin has many protective actions in the initiation and progression of atherosclerosis by means of direct anti-inflammatory and anti-atherogenic effects. Increased adiponectin is associated with improved insulin sensitivity and is a known enhancer of fatty acid metabolism. Unfortunately, obesity is associated with decreased levels of adiponectin, and decreased levels of adiponectin are associated with an increased risk of cardiovascular disease in humans.

Apelin and visfatin are 2 adipokines that are significantly up-regulated in the obese state and exert some beneficial effects, potentially protecting against obesity-related pathologies. Apelin exerts a potent and long-lasting positive inotropic effect, which is preserved in the failing myocardium and is accompanied by potent vasodilatation. Visfatin possesses insulin-like hypoglycemic properties. The studies on apelin and visfatin, like other adipokines, are only in their nascent stage, and many questions remain unanswered. Further research in this field will unearth many more answers and help us to better understand their relation to cardiovascular disease.

**SUMMARY**

In summary, obesity is associated with a wide variety of endocrine and metabolic abnormalities that may contribute to the development of heart and vascular disease. These alterations include activation of the renin-angiotensin system, stimulation of the sympathetic nervous system, the development of insulin resistance and hyperinsulinemia, elevated levels of free fatty acids, and increased circulating...
serum levels of leptin due to leptin resistance. Such pathophysiologic alterations alone or in combination may predispose to the development of hypertension, cardiovascular disease, myocardial and vascular smooth muscle hypertrophy, and congestive heart failure. Obesity also is associated with a proinflammatory and prothrombotic environment signified by the presence of elevated high-sensitivity CRP and PAI-1 levels. Such alterations may predispose to the development of acute coronary syndromes. Low serum levels of the adipocytokine adiponectin and elevated levels of acylation-stimulating protein also predispose to cardiovascular disease. Weight loss reverses many of these endocrine and metabolic effects of obesity and may potentially attenuate the risk for their cardiac and vascular sequelae.

References


