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Pathophysiological Processes Causing the Development of Obesity

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Annotation. *Obesity is an increase in body adipose tissue and an endocrine and metabolic disorder that has become epidemic worldwide. Obesity is defined differently in adults and children. In adults, it is a body mass index (BMI) that exceeds 30 kg/m^2. Obesity is an increase in body adipose tissue and an endocrine and metabolic disorder that develops when caloric intake exceeds energy expenditure. Obesity is an epidemic that has occurred worldwide in both adults and children. Single-gene (rare) and polygenic disorders and metabolic disorders are associated with obesity, as are gene–environment interactions. Adipokines and gastrointestinal hormones are altered with obesity and contribute to associated complications.*

Keywords. *obesity, endocrine system, adipokines, energy balance, fatty body, leptin, adinopectin, ghrelin*

Obesity of one of the most common and costly chronic diseases in the world. The causes are complex, multifactorial, and associated with an increased risk of many comordid diseases. Alternatively, starvation and anorexia of aging also are common conditions. The purpose of this article is to present an overview of the function of adipose tissue and the pathophysiology of obesity.

Adipose tissue provides insulation and mechanical support, secretes hormonelike signaling molecules known as adipokines, and contributes to immune cell function. It is the body's major energy reserve to fuel other tissues. Adipocytes are fat-storing cells that store calories in the form of triglycerides (triglycerol), synthesize triglycerides from glucose, and mobilize energy in the form of free fatty acids (FFAs) and glycerol. Adipose tissue is classified according to color as white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue (bAT). These tissue types are found in different locations and have different functions. Most adipose tissue in the body is WAT.

Adipose Tissue as an Endocrine Organ. Adipose tissue is also an endocrine organ, and adipocytes secrete adipokines. Adipokines are cell-signaling proteins that function like hormones, having autocrine, paracrine, and endocrine actions. Adipokines include all the biologically active substances synthesized by WAT. They are necessary for numerous functions in body tissues. These substances function in the regulation of appetite, food intake and energy expenditure, lipid storage, insulin secretion and sensitivity, immune and inflammatory responses, coagulation, fibrinolysis, angiogenesis, fertility, vascular homeostasis, blood pressure regulation, and bone metabolism. Excess WAT causes dysregulation of the secretion and function of adipokines, contributing to the many complications of obesity.

Regulation of Food Intake and Energy Balance Regulation of food intake and energy balance is a complex process controlled by central and peripheral physiological signals. Centrally, the arcuate nucleus (ARC) in the hypothalamus regulates food intake and energy metabolism by balancing the opposing effects of two sets of neurons. One set of neurons promotes appetite, stimulates eating, and decreases metabolism (anabolic). These are known as orexigenic neurons, which are stimulated by molecules called orexins. Another set of neurons suppresses appetite, inhibits eating, and increases metabolism. These are known as anorexigenic neurons, which are stimulated by molecules called anorexins. The hypothalamic orexin and anorexin signaling pathways are transmitted through the autonomic nervous and endocrine systems to regulate and balance appetite, food intake, energy metabolism, and body temperature. The hypothalamus also communicates with higher brain centers related to reward, pleasure, memory, and addictive behavior. These higher centers can override hypothalamic control of food intake and satiety, which increases consumption of highly palatable foods and results in increased fat stores. Peripherally, the gastrointestinal tract secretes a number of hormones that also control hunger and satiety. In addition, adipokines can function as orexins or anorexins and provide peripheral signals for the control of food intake and energy expenditure.

Obesity is an increase in body adipose tissue and an endocrine and metabolic disorder that has become epidemic worldwide. Obesity also is a risk factor for hypertension, stroke, hyperlipidemia, gallstones, nonalcoholic steatohepatitis (NASH), gastroesophageal reflux, hiatal hernia, osteoarthritis, infectious disease, asthma, obstructive sleep apnea, and chronic kidney disease. However, some studies have shown that mild obesity in older individuals is associated with lower mortality (the obesity paradox), but the mechanisms are not clear. The causes and consequences of obesity are multiple and complex, and rapidly advancing research is underway on the causal mechanisms complications, and treatment.

Genotype and gene–environment interactions are important predisposing factors. Single-gene defects (monogenic defects) are rare, and obesity is usually polygenic and associated with other phenotypes, such as endocrine disorders (i.e., diabetes mellitus and hypothyroidism) and mental retardation (i.e., Down and Prader-Willi syndromes). Metabolic abnormalities that contribute to obesity include Cushing syndrome, Cushing disease, polycystic ovary syndrome, growth hormone deficiency, hypothyroidism, and hypothalamic injury. Contributing environmental factors include food intake (low nutrient, energy-dense foods), physical inactivity, obesogens, and socioeconomic status (both high and low income). Obesity also is associated with adverse social and psychological consequences, including depression and mood disorders.

The pathophysiology of obesity is complex and involves the interaction of peripheral and central neuroendocrine pathways, numerous adipokines, hormones, and neurotransmitters. The adipocyte is the cellular basis of obesity. Excess fat is stored in mature white adipocytes when energy balance is positive (excess caloric intake in relation to energy expenditure). These adipocytes undergo hypertrophy and adipogenesis (hyperplasia), store triglycerol, and secrete adipokines. Adipokines circulate in the blood at concentrations that increase or decrease in relation to body fat mass and provide signals to the central nervous system for regulation of hunger, satiety, and energy balance, as described previously. WAT accumulation causes dysfunction in the regulation and interaction of this signaling system and contributes to the complications and consequences of obesity.

Adipokines and Obesity

Leptin is a product of the obesity gene (Ob gene) and is expressed primarily by adipocytes. Leptin levels increase after eating and act on the hypothalamus to inhibit orexigenic neurons and stimulate anorexigenic neurons to suppress appetite and increase energy expenditure. At low leptin levels (i.e., during fasting), leptin stimulates food intake and reduces energy expenditure. This balance regulates

body weight and energy expenditure within a fairly narrow range. Leptin levels increase as the number of adipocytes increases. However, high leptin levels are ineffective at decreasing appetite and energy expenditure, a condition associated with obesity and known as central leptin resistance. Leptin resistance fails to inhibit orexigenic hypothalamic satiety signaling and promotes overeating and excessive weight gain. Leptin also regulates hepatic gluconeogenesis, insulin sensitivity, and glucose and lipid metabolism in liver, muscle, and adipose tissue. Peripheral leptin resistance (i.e., in muscle and adipose tissue) results in hyperglycemia, hyperinsulinemia, and hyperlipidemia and also stimulates macrophages and endothelial cells to produce proinflammatory mediators. The cause of leptin resistance is unknown. It may be related to a defect in leptin transport, an inability of leptin to cross the blood–brain barrier, an alteration in the permissive effect of leptin, or a defect in or suppression of the leptin receptor. The low-grade inflammation that accompanies obesity also is thought to contribute to leptin resistance. Chronic hyperleptinemia also stimulates the sympathetic nervous system, oxidative stress, chronic low-grade inflammation, and ventricular hypertrophy and contributes to the pathogenesis of hypertension, atherosclerosis, cardiovascular disease, and cancer associated with obesity.

Adiponectin, which is produced primarily by visceral adipose tissue but also by cardiomyocytes and skeletal muscle, increases energy expenditure. It also has insulin-sensitizing and antiinflammatory properties. Plasma levels of adiponectin decrease with visceral obesity, and resistance to adiponectin action develops. Decreased adiponectin levels are associated with increased hepatic gluconeogenesis, insulin resistance, decreased skeletal muscle glucose uptake, and increased levels of inflammatory mediators, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Adiponectin serves as an antiinflammatory and antiatherogenic plasma protein; it also has an important role in vascular remodeling, and it is cardioprotective. Decreased levels of adiponectin are associated with type 2 diabetes mellitus and an increased risk for coronary artery disease resulting from hyperlipidemia, hypertension, and factors that promote thrombosis and inflammation. Decreased beta cell function and insulin resistance are associated with obesity. The mechanisms are not clear, but an association exists between hyperlipidemia and increased fat storage, macrophages and inflammation, and alterations in adipokines. Leptin resistance and decreased adiponectin also contribute to insulin resistance. Insulin resistance results in hyperinsulinemia, hyperglycemia, and a predisposition to type 2 diabetes mellitus. Retinol-binding protein 4 (binds vitamin A) is an adipokine produced both in the liver and by adipocytes. It is increased in visceral adiposity and contributes to inflammation and insulin resistance in the liver and muscles; it also is associated with hepatic steatosis (fatty liver) and cardiovascular disease.

Endocannabinoids (i.e., anandamide) are arachidonic acid derivatives (unsaturated, essential fatty acids) expressed in both the brain and peripheral nerve tissues. They have effects on endocannabinoid (CB) receptors in orexigenic pathways. They increase appetite, enhance nutrient absorption, stimulate lipogenesis, and increase WAT accumulation by acting at both central (CB1 receptor) and peripheral sites (CB2 receptor). They also inhibit energy expenditure and thermogenesis. An increase in endocannabinoids is proposed to be associated with obesity.

Angiotensinogen (AGT) is produced in the liver and by adipocytes and is increased in obesity. AGT is the precursor to angiotensin 1 (AGTI), which is then converted to angiotensin 2 (AGTII). The effects of AGTII include vasoconstriction, renal retention of sodium and water, and release of aldosterone. Increased AGTII from adipose tissue also promotes lipogenesis, oxidative stress, inflammation, and insulin resistance. All of these effects contribute to the complications associated with obesity.

Ghrelin is produced by the stomach gastric mucosa. It increases in response to fasting and chronic caloric restriction and decreases after food intake. Ghrelin stimulates food intake and fat storage and prevents life-threatening falls in blood glucose. Ghrelin is thought to have antilipolytic effects and

stimulates lipogenesis in visceral WAT, leading to an increase in body weight and body fat mass. Ghrelin also stimulates the release of growth hormone (GH) from anterior pituitary cells, the release of gastric acid, gastrointestinal motility, and pancreatic secretion of insulin. It has satiety, vasodilatory, and cardioprotective effects. An elevation in FFAs and GH after eating normally decreases the release of ghrelin. However, obesity is associated with a decreased plasma level of ghrelin, and plasma ghrelin levels do not fall after eating. This is known as ghrelin resistance. The mechanisms for this response are not clear, and the role of ghrelin in obesity has yet to be clearly defined.

Glucagon-like peptide 1 (GLP-1) is an anorexigenic hormone secreted by intestinal endocrine cells when nutrients enter the small intestine. GLP-1 stimulates pancreatic glucose-dependent insulin secretion, decreases blood glucose levels, delays gastric emptying, suppresses appetite, increases satiety, and increases energy expenditure. GLP-1 levels may be decreased in obese individuals, and a GLP-1 receptor analogue has been approved to treat both obesity and type 2 diabetes mellitus.

Peptide YY (PYY) is released from intestinal endocrine cells in response to nutrients entering the intestine. PPY inhibits gastric motility and decreases appetite; it decreases with obesity.

Cholecystokinin (CCK) is secreted by proximal small intestinal cells after food intake. Its actions include gallbladder contraction, release of pancreatic enzymes and insulin, satiation, and reduced food intake. CCK is reduced in obesity.

All in all, Obesity usually presents with two different forms or phenotypes of adipose tissue distribution: visceral and peripheral. Visceral obesity (also known as intra-abdominal, central, or masculine obesity) occurs when the distribution of body fat is localized around the abdomen and upper body, resulting in an apple shape. Visceral obesity is associated with accelerated lipolysis and has an increased risk for chronic systemic inflammation, metabolic syndrome, obstructive sleep apnea syndrome, type 2 diabetes mellitus, cardiovascular complications, osteoarthritis, and cancer. Visceral venous blood drains into the portal vein, contributing to higher liver synthesis of plasma lipids and increasing the risk of NASH. Peripheral obesity (also known as subcutaneous, gluteal-femoral, or feminine obesity) occurs when the distribution of body fat is extraperitoneal and distributed around the thighs and buttocks and through the muscle, resulting in a pear shape; it is more common in premenopausal women**.**

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