

# Metabolic effects associated with adipose tissue distribution

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## Abstract

Cardiovascular and metabolic risk depends not only on the overall obesity but also fat distribution is more powerful predictor for risk factors. Adipose tissue produces and secretes a variety of bioactive peptides – adipokines

The most recently described adipocyte secretory proteins contribute to the pathogenesis of impaired insulin secretion and insulin resistance, endothelial dysfunction, a proinflammatory state and promote progression of atherosclerosis. This review presents an overview of the adipose tissue secreted proteins (leptin, TNF- $\alpha$ , IL-6, adiponectin, resistin, visfatin, ASP, FIAF, MT) role and their regulation in the context of abdominal obesity and the adverse metabolic consequences.

**Key words:** adipose tissue, abdominal obesity, adipokines.

Obesity causes a significant increase in the morbidity and mortality rate. Obese persons are predisposed to hypertension, dyslipidaemia, diabetes mellitus and coronary heart disease [1]. Cardiovascular and metabolic risk depends not only on the overall obesity but also the fat distribution is more powerful predictor for risk factors. Waist circumference – a convenient measure of abdominal adipose tissue, is a better predictor than BMI and waist-to-hip ratio [2]. The waist circumference is measured in the horizontal plane midway in the distance of the superior iliac crest and the lower margin of the last rib. The prevalence of obesity increases and the most alarming is markedly growing prevalence of abdominal obesity [3].

Previously, adipocytes were considered to be an inert storage depots, storing fats as triglycerides in the fed state, and releasing fuel as fatty acids and glycerol in times of fasting [4]. Intra-abdominal adiposity liberates fatty acids directly to the portal vein, and so they have direct effects on liver metabolism. It is associated with insulin resistance leading to hyperinsulinaemia and increased hepatic triglyceride synthesis.

In the state of elevated triglycerides, LDL particles become enriched in triglycerides, which are hydrolyzed to small dense LDL particles. Increased plasma triglycerides are also associated with reduced HDL levels [5].

Adipose tissue is now known to secrete a variety of bioactive peptides – adipokines [6-8]. They act at both the local (autocrine/paracrine) and systemic (endocrine) level. Direct adverse effects of intra-abdominal adiposity occur via secretion of a range of bioactive substances. The most recently described adipocyte secretory proteins contributed to the pathogenesis of impaired insulin secretion and insulin resistance, endothelial dysfunction, contributes to a proinflammatory state and promotes progression of atherosclerosis [9]. Leptin, tumor necrosis factor (TNF- $\alpha$ ) and interleukin-6 secreted by intra-abdominal adiposity increases insulin resistance [6].

**Leptin**, secreted predominantly from adipocytes, interacts with several central neuroendocrine systems, including neuropeptide Y leading to the inhibition of food intake. Leptin induced increase in renal sympathetic activity and blood pressure are mediated by the hypothalamic melanocortin system. Circulating leptin level is positively correlated with the body mass index. Centrally, it is capable of altering food intake, body weight, energy expenditure, and neuroendocrine function, whereas it has also peripheral effects on skeletal muscle, liver, pancreas, and other tissue. Leptin affects a diverse spectrum of metabolic processes. Leptin serves as a metabolic signal of energy sufficiency. Catecholamines inhibit leptin synthesis while leptin stimulates the sympathetic nervous system, decreases insulin sensitivity, and contributes to the development of hypertension. Leptin accelerates puberty and restores normal

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gonadotropin secretion and reproductive function. Important effects of leptin include the regulation of immune function, hematopoiesis, angiogenesis and the bone development [10].

**Tumor necrosis factor (TNF- $\alpha$ )** is a cytokine mainly produced by macrophages; adipocytes are also a significant source of TNF- $\alpha$ . TNF- $\alpha$  inhibits tyrosine kinase dependent phosphorylation of the insulin receptor, resulting in defects in insulin signaling and leading to insulin resistance and impaired glucose transport [11].

TNF- $\alpha$  decreases activity of lipoprotein lipase and increases hormone-sensitive lipase, preventing lipid accumulation. TNF- $\alpha$  exerts its effect on cell function by binding to two specific cell surface type I and type II receptors. The extracellular portions of this membrane receptors are separated from them and circulate as soluble forms. TNF- $\alpha$  expression in the adipose tissue and serum levels are elevated in obesity. The observed decrease of the serum concentration of TNF- $\alpha$  and the increase in both soluble receptors after weight reduction in obese women may be a counter-regulation preventing further weight loss [12].

**Interleukin-6 (IL-6)** has also proinflammatory activity. Both adipose tissue expression and circulating levels are correlated with obesity, impaired glucose tolerance and insulin resistance. IL-6 stimulates the liver production of CRP – important marker of vascular inflammation and predictor of atherosclerosis [8].

**Adiponectin** is an adipocyte-derived plasma protein with the insulin sensitizing properties. In the liver, it increases fatty acids oxidation and reduces hepatic glucose output. In the muscle, adiponectin stimulates glucose use and fatty acids oxydation. Within the vascular wall it inhibits monocyte adhesion, inhibits macrophage transformation to foam cells, increases nitric oxide production in endothelial cells. Adiponectin is a unique adipokine with antidiabetic, antiinflammatory and antiatherogenic effect. Circulating adiponectin level is reduced in obesity [13] and increases after weight loss [14].

**Resistin** is secreted from adipocytes. It contributes to insulin resistance [15]. Increased resistin expression in abdominal adipose tissue compared with thigh fat could explain the increased risk of diabetes associated with abdominal obesity [16,17].

**Visfatin** is adipokine expressed at high levels in visceral fat [18]. Visfatin stimulates glucose uptake by adipocytes and muscle cells and suppresses glucose release by hepatocytes. Visfatin binds to the insulin receptor at a different site from insulin. This cytokine exerts insulin-mimetic effects by lowering plasma glucose level. Like insulin, visfatin induces fosforylation of signal transduction proteins that operate downstream of the insulin receptor. Mice on the high-fat diet had higher plasma visfatin concentrations compared to mice fed normal chow. Plasma visfatin concentration increases during the development of obesity. Visfatin levels in serum increases parallelly with visceral but not subcutaneous fat [19]. So far only in few studies visfatin expression in adipose tissue and plasma concentration in human were assessed [20].

Our results [21] have shown an increased serum concentration of visfatin in obese women compared to controls. It may be one of counter-regulatory mechanism preventing the glucose increase during development of insulin resistance accompanying the visceral obesity.

**Acylation-stimulating protein (ASP)** is produced from three precursor proteins of the alternate complement system: C3, factor B and adipsin, which are secreted by adipocytes. ASP increases lipogenesis locally in adipocytes and inhibits hormone-sensitive lipase – mediated lipolysis. ASP level is elevated in obese humans and decreases after fasting or weight loss.

**Fasting-induced adipose factor (FIAF)** concentration increases in plasma on fasting and decreases on feeding a high-fat diet. It has been speculated that FIAF operates reciprocally to leptin.

**Metallothionein (MT)**, a stress-response and metal-binding protein is synthesised particularly in the liver and kidneys. Recently MT-1 and MT-2 genes expression in adipocytes was demonstrated. The expression of the MT gene can be subjected to the adrenergic activation and was stimulated by the agents which increase cAMP. The main function of MT in adipose tissue may be an antioxidant protection of fatty acids from the oxidative damage [4].

The adverse effects of intra-abdominal adiposity occur via an increased secretion of plasminogen activator inhibitor-1 (PAI-1) which increases the risk of an intravascular thrombosis. Activation of the renin-angiotensin system and increased angiotensinogen secretion is involved in the development of hypertension in visceral obesity [9].

Obesity is associated with an increased storage of lipids in non-adipose tissue like skeletal muscle, liver and pancreatic  $\beta$  cells. Lipid accumulation in non-adipose cells may lead to the cell dysfunction – **lipotoxicity** [22].

Steatosis hepatis (NAFLD = non-alcoholic fatty liver disease) is found in about 60% of the obese patients, whereas NASH = non-alcoholic steatohepatitis in from 20% to 25% of obese and between 2% and 3% of obese have liver cirrhosis.

Exposure of pancreatic  $\beta$  cells to high level of fatty acids increases insulin secretion. Long time exposure to fatty acids leads to  $\beta$  cells dysfunction, increased synthesis of ceramide and apoptosis. Long-term effect represents the transition from insulin resistance and glucose intolerance to overt diabetes [23].

The causes of cardiac dysfunction in obesity could be related to frequently observed hypertension and increased cardiac output; additional work load, cardiac hypertrophy and accumulation of fat pads around ventricles, which increase ventricular stiffness and contribute to diastolic dysfunction. Cardiac intramyocytic lipid accumulation may trigger apoptosis and systolic dysfunction [24].

Obesity is associated with endothelial dysfunction. Endothelial dependent vasodilatation is impaired in proportion to insulin resistance. Visceral obesity is characterized by impaired NO-dependent relaxation in the large arteries and also loss of NO-independent, potassium-mediated relaxation in the small

Table 1. Metabolic phenotypes

	Amount of visceral fat	Insulin sensitivity	Plasma triglycerides
Obese with metabolic risk	high	low	high
Normal weight metabolically obese	high	low	high
Obese metabolically healthy	low	high	low
Normal weight metabolically healthy	low	high	low

arteries. Visceral obesity is a powerful predictor of coronary artery atherosclerosis [25].

Cardiovascular risk is connected with several classical risk factors, such as hypertension, hypercholesterolaemia, smoking and very important factor – abdominal obesity [26]. Adipose tissue produces and secretes inflammatory factors, which play important role in the atherosclerotic process. Abdominal obesity is often associated with other cardiovascular risk factors: hypertriglyceridaemia, low HDL-cholesterol, insulin resistance and hyperglycaemia.

The criteria of the **metabolic syndrome** from the IDF (International Diabetes Federation, 2005) requires the presence of high waist circumference, alone and two other cardiovascular risk factors among following:

- triglycerides >150 mg/dL (1.7 mmol/L)
- HDL cholesterol men <40 mg/dL (1.0 mmol/L)  
women <50 mg/dL (1.3 mmol/L)
- blood pressure >130/85 mmHg
- glucose >100 mg/dL (5.6 mmol/L) or diabetes

The ethnic-group specific values for waist circumference are provided

- for European men >94 cm and women >80 cm.

The risk factors recognised as criteria for the diagnosis of the metabolic syndrome [27] and novel risk factors such as chronic low grade inflammation and disturbances in the secretion of bioactive substances from adipocytes – adipokines contribute to the progression of atherosclerotic cardiometabolic disease. A triad of “new” atherogenic metabolic risk markers – fasting hyperinsulinaemia, increased apolipoprotein B concentration, and an increased proportion of small, dense low density lipoprotein particles observed in viscerally obese patients with insulin resistance is associated with a marked increase in the risk of coronary heart disease. Simple screening variables, such as waist circumference and fasting triglyceride concentrations identify high risk, viscerally obese patients who could be carriers of the atherogenic triad [28].

Abdominal obesity increases the risk of the developing of type 2 diabetes and metabolic syndrome [29,30]. Subjects with the metabolic syndrome were between 2 and 3 times more likely to die from an adverse cardiovascular events and three times likely to have heart attack or stroke compared to people without the metabolic syndrome [31].

According to the INERHEART Study abdominal obesity is a major cause of acute myocardial infarction [32]. In the Heart Outcomes Protection Evaluation (HOPE) Study the risk of cardiovascular death, myocardial infarction, or death from any cause increased proportionally with increasing tertiles of waist circumference [33].

During 8 years of follow-up, the prospective Nurses Health Study shows relationship between the waist circumference and risk of cardiovascular disease [34].

Body fat distribution abnormalities may play an important role in the development of metabolic complications. The amount of visceral fat is associated with a decrease of insulin sensitivity, which could lead to an increase risk of cardiovascular disease.

**Metabolic phenotypes** [35] were identified due to amount of visceral fat, insulin sensitivity, plasma triglycerides (Tab. 1). Two subtypes of individuals were identified:

- 1) “metabolically obese” among obese and also normal weight persons,
- 2) “metabolically healthy” among normal weight persons and obese with normal insulin sensitivity.

Identifying the physiological and behavioral factors that could be used to classify an individual as “metabolically obese” or “metabolically healthy” would be valuable and could have important therapeutic implications.

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