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Role of adipokines in complications related to obesity. A review

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ABSTRACT

Worldwide, the prevalence of overweight and obesity and associated complications is increasing. Cardiovascular complications are the most important factor determining survival and influencing clinical management. However, obesity is also associated with an increased risk of metabolic syndrome, type 2 diabetes, cancer and other diseases. The development of complications depends on the amount of body fat and its endocrine function. The hormones (leptin, adiponectin, resistin) and cytokines (TNF alpha, IL-6, PAI-1) produced by the adipose tissue are the link between obesity and obesity-related complications. The present article discusses the structure, function and clinical significance of adipokines.

Key words: adipokines, obesity, metabolic complications

INTRODUCTION

Obesity is a chronic disease affecting over a billion adults all over the world. It is predicted that its prevalence will have doubled by the year 2030 and that the obesity epidemic is going to become the biggest health problem of our century. Moreover, with increasing number of patients suffering from obesity, the prevalence of complications resulting from the excess of adipose tissue is growing [1-3].

It is known nowadays that the adipose tissue is the place of synthesis of many metabolically active proteins known as "adipokines" or "adipocytokines".

Adipokines play a significant role in the regulation of local metabolic processes (autocrine and paracrine function). They also regulate systemic processes, displaying typical endocrine properties. Therefore, adipose tissue is an important part of the endocrine system [4-7]. Adipocytes are not the only cells displaying endocrine properties. Other cells, e.g. the abundantly present macrophages have also been found to play a role.

REVIEW

The adipose tissue was recognized as an active endocrine organ that can affect the function of other organs and an important source of several proinflammtory cytokines, chemokines, growth factors and complement proteins called "adipokines". It is already known that mature adipocytes are the main source of leptin and adiponectin, macrophages produce almost all TNF-α, resistin and visfatin, while prostaglandin E2, interleukins, vascular endothelial growth factor, hepatocyte growth factor are synthesized by stromal and vascular cells.

So far as many as 100 substances synthesized by the adipose tissue (preadipocytes, adipocytes as well as other cell types) have been discovered. They are responsible for the interactions between the adipose tissue, muscular tissue, adrenal cortex and the central and sympathetic nervous systems. They take part in keeping the energetic balance of the organism, determining insulin sensitivity as well as in regulating blood pressure, the immune response, angiogenesis, lipid metabolism and hemostasis. The main role of white adipose tissue is presented on *Fig1*.

Figure 1. **Physiological and metabolic processes which white adipose tissue is involved through the secretion of adipokines.**

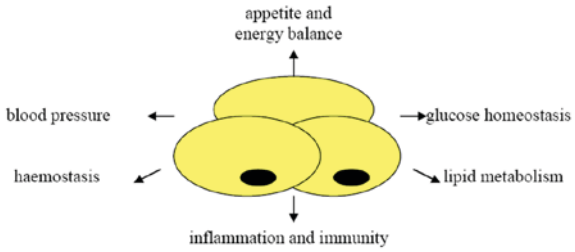
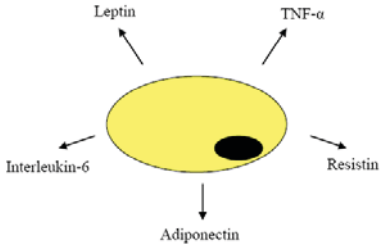


Figure 2. **The main adipokines and cytokines which have been implicated in the pathogenesis of insulin resistance and obesity.**



Adipose tissue produce following adipokines:

- cytokines and cytokine-related proteins:
  - leptin
  - tumor necrosis factor α (TNF-α)
  - interleukin 1 ß, 4, 6, 8, 10, 18
- proteins related to immune system:
  - macrophage chemoattractant protein (MCP-1)
  - metallothionein
  - macrophage migration inhibitory factor (MIF)
- proteins related to fibrinolysis:
  - plasminogen activator inhibitor 1 (PAI-1)
  - tissue factor (TF)
- proteins related to complement:
  - adipsin (complement factor D)
  - adiponectin
- proteins connected with lipid metabolism and transport
  - lipoprotein lipase (LPL)
  - cholesteryl ester transfer protein (CETP)
  - apolipoprotein E
  - insulin growth factor (IGF-1)
  - adipocyte fatty acid-binding protein (aP2)
  - retinol-binding protein (RBP)
- enzymes
  - aromatase cytochrome p 450
  - dehydrogenase 17 ß -hydroksysteroid (17 ß-HSD)
  - dehydrogenase 11 ß-hydroksysteroid type 1 (11 ß-HSD1)
- components of renin-angiotensin system:
  - renin
  - angiotensynogen
  - angiotensin I, II
  - angiotensin converting enzyme (ACE)
- proinfalmmatory adipokines:
  - resistin
  - apelin
  - visfatin
  - nerves growth factor (NGF)
  - TNF-α, interleukin- 6, IGF-1, adiponectin

Adipose tissue presents following receptors:

- hormones receptors:
  - insulin
  - glucagon / cholecystokinin B (CCK-B)
  - thyroid stimulating hormone (TSH)
  - gastrine
  - glucagon like peptide 1
  - angiotensin II (receptor type 1 i 2)
  - glicocortycoids
  - androgens
  - estrogens
  - progesteron
- cytokins receptors:
  - leptin
  - interleukin 6
  - TNF-α
- catecholamines receptors:
  - ß 1, ß 2, ß 3
  - α 1, α 2
- and also
  - resistin receptors
  - perioxisome proliferator activated receptor γ (PPAR γ) [5-7]

It is the excess of visceral adipose tissue and increase production of adipokines are mostly responsible for metabolic complications. The main adipokines which have been implicated in the pathogenesis of insulin resistance and obesity are presented on *Fig.2*.

The main components of metabolic syndrome are abdominal obesity with insulin resistance, hyperinsulinemia, high blood pressure, dyslipidemia, hyperglycemia and type 2 diabetes mellitus. The other elements of that syndrome are hyperuricemia and proinflammatory status.

The presence of metabolic syndrome is associated with a threefold increase in the risk of cardiovascular complications, most commonly ischaemic heart disease and stroke. The so-called cardiometabolic syndrome is being increasingly recognized in medical literature [8-11].

Other consequences of obesity include heart failure, endocrine disorders (hyperandrogenemia, polycystic ovary syndrome), obstructive sleep apnea, restrictive ventilation disorder, cholecystolithiasis, fatty liver and gastroesophageal reflux disease. Obesity is also a risk factor for malignant tumors, with cancers of the prostate, gallbladder, kidney and pancreas commonly affecting men and tumors of the endometrium, cervix, ovary, breast and large intestine more prevalent in women [8,12].

Since the 1980s it has been emphasized that inappropriate diet, lack of exercise and sociocultural influence are not the only factors responsible for the development of metabolic syndrome but that genetic factors also play a role. Groop and others described in detail the genetic factors in the development of obesity and emphasized the sociocultural influence [13].The most recent studies on the metabolic syndrome and insulin resistance focus on such factors as subclinical inflammatory process and hormonal activity of the adipose tissue [14].

Obesity and inflammation

The adipocyte is the site of synthesis for many proteins involved in inflammation. Cytokines associated with inflammation and secreted by adipocytes include TNF-α, interleukins (IL-1β, IL-6, IL-8, IL-10), the monocyte chemotactic protein 1 (MCP-1) and macrophage migration inhibitory factor (MIF). Adipocytes also secrete acute phase proteins such as amyloid A, haptoglobin, PAI-1 and ASP. Adipokines such as leptin, resistin, vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) also play a role in inflammation. The concentration of most pro-inflammatory cytokines (which are produced by macrophages and adipocytes) increases along with the growth of fat body mass. Therefore obesity may be characterized by a co-existing chronic, benign inflammatory state. Nevertheless adipose tissue is the source of ongoing inflammatory process. Inflammation may play a leading role in the development of insulin resistance and metabolic syndrome [15,7,16-18].

Metabolic processes and immune system are closely related. Both excessive food intake and malnutrition can affect the immune system. Malnutrition which causes immunosuppression leads to higher susceptibility to infections whereas obesity is associated with inadequate immune reaction and increased risk of inflammatory diseases such as diabetes and atherosclerosis. Balanced nutrition is the only way to maintain adequate function of the immune system. The mechanism of inflammation in obesity is similar as in malignant and autoimmune diseases [19].

Adipokines and the development of obesity complications

Nowadays it is assumed that unfavorable changes in the secretion of adipose tissue hormones and inflammatory cytokines caused by obesity influence the development of metabolic syndrome and vascular complications. Since the discovery of leptin, research on the etiology of obesity - related diseases has been directed at the metabolic and endocrine function of the adipose tissue [20].

Adipokines are important determinant of insulin sensitivity and thus a potential link between obesity and insulin resistance [21,22]. Additionally, increased concentration of interleukin-6 and TNF-α is responsible for insulin resistance [12] as well as endothelium dysfunction [23].

Leptin and adiponectin are adipokines which increase tissue sensitivity to insulin. Both adipokines stimulate the oxidation of fatty acids thus decreasing the amount of accumulated triglycerides. The increased concentration of leptin in obesity does not lead to improved tissue sensitivity to insulin because of the development of leptin resistance.

The concentration of adiponectin decreases with increasing body fat content, precluding their beneficial effect on insulin sensitivity and preventing vascular injury [24,21].

Role of leptin in obesity and insulin resistance

Leptin is a product of the obesity gene (ob) which was discovered in 1994 in obese mice ob/ob by Zhang and co-workers [25]. Almost at the same time the ob gene was discovered in humans on chromosome 7q31. The product of that gene was called leptin (Greek *leptos* meaning slim). Leptin regulates the intake of food by decreasing appetite. Its acts within the central nervous system but its role is not restricted to the regulation of energy balance [25].

The first data about the physiological role of leptin and its significance in the development of insulin resistance come from studies in animals lacking this hormone. A mutation in the ob/ob obesity gene in mice causes lack of leptin, leading to hyperphagia, obesity and, subsequently, to the development of insulin resistance and endocrine disorders. The administration of recombined leptin in these animals decreases food intake, increases basic metabolism and leads to significant body mass reduction. Moreover, it also increases their physical activity and decreases serum insulin concentration [26-29].

Interestingly, with leptin administration normal glucose and insulin metabolism is achieved before body mass reduction, suggesting that the influence of leptin on glucose homeostasis may be independent from its effect on body mass reduction [30]. db/db mice and fa/fa rats have a mutation of leptin receptor coding gene. This defect causes lack of response on leptin even if its concentration is normal. The observed fenotypical effect is similar to that seen in ob/ob mice. Obviously, exogenous leptin administration will not be sufficient in this case [29,31]. It was expected that the discovery of mutation in the leptin and leptin receptor genes would lead to a better understanding of the causes of obesity.

It is not the absolute deficiency of leptin that causes obesity as the concentration of leptin actually increases in the setting of obesity, but rather the lack of sensitivity to its action [25,32]. Obese people have a higher concentration of leptin which at the same time seems not to show the desirable anorexic effect because of leptin resistance.

Disorders of transport to the brain, the presence of anti-leptin antibodies or leptin antagonists are considered as possible mechanisms. There are some experimental data for occurrence of leptin resistance since leptin induces the expression of SOCS3 (suppressor of cytokine signaling), which prevents that cells from responding to further leptin. But exact mechanism of leptin resistance is however still unknown [25,33].

Both leptin and insulin acting at the level of the central nervous system decrease food intake and increase energy

expenditure. Both hormones regulate long term energy homeostasis [34]. Insulin stimulates production of leptin by influencing glucose metabolism. Leptin, via a negative feed-back, decreases the secretion of insulin and inhibits expression of its gene. Hyperleptinemia associated with obesity is currently considered to be an important factor in the development of type 2 diabetes mellitus. Leptin resistance has also been demonstrated in pancreatic beta cells, where it leads to deregulation of the adipocyte-insulin axis. The resulting hyperinsulinemia stimulates adipogenesis which leads to a further increase in insulin secretion. The consequence is a dysfunction of pancreatic ß cells and the development of clinical diabetes [35,36].

Adiponectin in obesity and insulin resistance

Adiponectin was independently discovered in the 1990s by four different research teams. For this reason it is known under different names in professional literature: Acrp30 (adipocytes complement-related protein of 30 kDa), AdipoQ, GBP28 (gelatin binding protein of 28 kDa) and apM1 (adipose most abundant gene transcript 1).

Adiponectin is produced predominantly by the adipose tissue. Its concentration, unlike that of other adipokines, is lowered in obesity and insulin resistance [37,38,16,39]. Hypoadiponectinemia is associated with the occurrence of metabolic syndrome, type 2 diabetes mellitus, hypertension, dyslipidemia, fatty liver disease and ischemic heart disease [40-43].The concentration of adiponectin is inversely proportional to the severity of coronary stenosis [44].

Elevated leptin level and decreased level of adiponectin are characteristic for the metabolic syndrome and correlated to high risk of cardiovascular diseases. A study by Lindsay et al [45] found no significant association between plasma adiponectin levels and risk of chronic heart disease in a nested case-control study among 372 American Indians after adjustment for other cardiovascular risk factors (odds ratio for 1-SD change in adiponectin, 0.90; $p = 0.34$). However, in stratified analyses, they found a significantly reduced risk among those with type 2 diabetes (comprising about 61% of their initial data set; odds ratio, 0.40; $p = 0.02$). Some authors suggested that plasma adiponectin levels may predict cardiovascular events years in advance in a population without diagnosed cardiovascular disease [45]. In fact, there are reasons to believe that adiponectin may not only be a marker of cardiovascular risk but also a causal risk factor. Adiponectin may lower the risk of cardiovascular disease by improving insulin sensitivity and blood lipid levels, as suggested by data from animal and human studies [46].

Therefore adequate adiponectin secretion prevents the development of diabetes and ischemic heart disease. In view of the advantageous metabolic effects of this protein, it is hoped that adiponectin can, in future, be used therapeutically [37,40]. Drugs such as thiazolidinediones, renin-angiotensin system blocking agents and antagonists of type 1 cannabinoid receptors (rimonabant) [47] can increase the concentration of adiponectin.

Resistin in obesity and insulin resistance

Resistin was discovered independently by three research teams. The first information about resistin was published in the year 2001. It owes its name to its observed influence on insulin resistance (resistin– resistance to insulin). This protein is also known as FIZZ3 (found in inflammatory zone) and ADSF (adipocyte-specific secretory factor) [21,48,49].

Resistin has a completely different structure from other adipokines. The resistin particle is made up of 108 amino acids and is rich in cysteine. The high cysteine content is characteristic for the whole group of proteins called resistin-like molecules (RELMs). There is still discussing where resistin is produced in humans, but it now seems clear that many different cell types secrete this peptide, with predominance of immuno-competent cells [50].

The role of resistin in obesity and insulin resistance remains unclear. Increased resistin concentration and/or increased expression of resistin mRNA in obesity and insulin resistance have been shown in some but not all studies. Studies in mice have shown that resistin administration leads to decreased insulin sensitivity. Similarly, increased resistin concentration has been observed in mice with genetic and diet-induced obesity [51,52]. In persons with obesity, the amount of resistin mRNA in adipose tissue, especially visceral adipose tissue is significantly higher compared to persons with normal weight [48,49,52]. However several human studies have also failed to demonstrate any impact of obesity and insulin resistance on the concentration of resistin [51,52].

Studies conducted so far show that the target organs for resistin are the liver, adipose tissue and skeletal muscles. Resistin increases hepatic glucose production and decreases the uptake and metabolism of fatty acids in skeletal muscles. It is presumed that resistin may be an important factor in the pathogenesis of metabolic disturbances. However its exact mechanism of action remains unknown [49,52].

It is assumed that resistin has a pro- inflammatory function. High concentrations of resistin in synovial fluid, positively correlated with markers of inflammation, were found in patients with rheumatoid arthritis. Of note, the family of RELM proteins was discovered during research on experimental asthma models (the other name of resistin-FIZZ3 – found in inflammatory zone - comes from this research) which indicates a proinflammatory action of resistin [52,53].

TNF–α in obesity and insulin resistance

The role of TNF–α in the development of insulin resistance has been demonstrated in various animal obesity models [54]. The neutralization of TNF–α significantly improved insulin sensitivity [55]. The expression of TNF–α mRNA in adipose tissue increases in obesity and hyperinsulinemia [53].TNF–α expression is higher in subcutaneous than in visceral adipose

tissue [5]. Some authors conclude that the serum concentration of TNF–α increases proportionally to the expression of mRNA in adipose tissue [56].The endocrine properties of TNF–α have been questioned and it has been suggested that it acts locally rather then systemically [5,16]. The increased synthesis of TNF–α in obesity limits body mass gain through lipolysis and, sometimes, through apoptosis of fatty cells. Moreover overproduction of this cytokine maintains and intensifies the inflammatory process leading to insulin resistance [56,57].

From the clinical point of view the important implications are the possibility of pharmacological modification of TNF–α concentration and consequently influencing the adverse effects of this cytokine. In *in vivo* studies the use of PPAR-gamma antagonists led to decreased tissue expression and serum concentration of TNF–α. Therapy with simvastatin is associated with lowering the level of such proinflammatory proteins as CRP and TNF–α. Moreover, the use of fibrates is probably associated with decreased TNF–α and interleukin-6 synthesis [58]. The administration of TNF-α inhibitors (etanercept, infliximab and adalimumab) in clinical practice has led to improved control of inflammation in rheumatoid diseases. However, administration of these antibodies to obese patients with type 2 diabetes does not influence insulin resistance [53,59]. Both body mass reduction and physical activity decrease the serum TNF –α level [54].

Interleukin - 6 in obesity and insulin resistance

About 30 % of circulating IL-6 comes from adipose tissue and this amount increases proportionally with increasing body mass. IL-6 expression in adipose tissue and its concentration in serum correlate positively with both obesity and insulin resistance [5]. The correlation between IL-6 and insulin resistance has also been found in cancer patients [20]. Serum IL-6 level is even three times higher in patients with obesity and type 2 diabetes than in slim people. The expression and secretion of this cytokine is two or three times higher in visceral than in subcutaneous adipose tissue. Administration of IL-6 causes hyperglycemia and insulin resistance. The polymorphism of IL-6 gene predisposes to disorders of carbohydrate metabolism. High serum concentration of this cytokine is a risk factor for type 2 diabetes and cardiovascular diseases. Body mass reduction results in decreased expression and concentration of IL-6 [5,21]. Surprisingly, physical activity also results in increased IL-6 level, most probably due to increased production by muscle tissue [60].

The mechanism by which IL-6 results in insulin resistance has not been explained so far. This cytokine decreases the expression of insulin receptors in peripheral tissues. It acts as an inhibitor of adipogenesis and inhibits adiponectin secretion. Another target organ for this cytokine is the liver, where IL-6 inhibits glycogen synthesis and activates lipolysis. Therefore increased insulin resistance may be linked to increased FFA production. It is supposed that IL-6 adversely influences the metabolism of carbohydrates through impact on visfatin regulation. The stimulation of the hypothalamic-hypophyseal-adrenal cortex axis by IL-6 may also increase insulin resistance [5,21,20,60].

CRP in obesity and insulin resistance

Studies addressing the relationship between the concentration of CRP and the presence of obesity and insulin resistance are much less numerous than those concerning CRP as a marker of cardiovascular complications. A positive correlation between the body mass index (BMI), waist-to-hip ratio (WHR) and CRP values has been described. Therefore obesity and metabolic disorders correlate with an increased risk of cardiovascular complications [61]. Increased CRP concentration is observed in patients with metabolic syndrome and insulin resistance. The correlation between CRP concentration and insulin resistance is independent from body mass. The CRP concentration correlates not only with the concentration of triglycerides, blood pressure and fasting glucose which are components of metabolic syndrome but also with endothelium dysfunction and fibrinolysis related to these metabolic disturbances. Increase in CRP level precedes the development of type 2 diabetes [62].Measurement of CRP concentration provides additional information about the risk of complications in patients with recognized metabolic syndrome. *Ridker* has proposed CRP to be included in the definition of metabolic syndrome [63].

PAI-1 in obesity and insulin resistance

Several studies have shown a correlation between PAI-1 concentration and BMI in all age groups, both in men and women. Obese people have an increased PAI-1 concentration in comparison to people with normal body mass. Moreover research confirmed increased expression of PAI-1 mRNA in adipose tissue in persons with obesity. A direct correlation between the expression of PAI-1 in adipocytes and its serum concentration has been observed. [64,65]. PAI-1 expression is higher in visceral as opposed to subcutaneous adipose tissue. Visceral type obesity is associated with increased PAI-1 concentration. Several studies, however have demonstrated no difference i in PAI-1 expression between visceral and subcutaneous adipose tissue. Eriksson and others found that subcutaneous adipose tissue shows higher expression of the PAI-1 gene than visceral adipose tissue [64-66].

Higher PAI-1 level co-exists with almost all components of metabolic syndrome, including hyperinsulinemia, visceral obesity, hypertension, hypertriglyceridemia, increased FFA concentration, increased LDL cholesterol and decreased HDL cholesterol concentration. The strongest correlation is shown with insulin and triglyceride levels, however few studies show that insulin resistance, proinsulin concentration and hyperglyceridemia independently determine the PAI-1 level. High concentration of PAI-1 is an independent risk factor for the development of type 2 diabetes. People with type 2 diabetes have a three times increased PAI-1 concentration compared to healthy people [66].

PAI-1 is recognized as an independent risk factor for cardiovascular diseases. Increased PAI-1 concentration precedes the development of cardiovascular complications and is present before clinical symptoms occur. The importance of PAI-1 is solely due to its role in thrombosis. PAI-1 plays an important role in the development of atherosclerotic disorders. It influences the formation of atheroma and makes it especially prone to injury. Therefore high PAI-1 concentration predisposes to acute coronary syndrome [66].

Similarly to most other cardiovascular risk factors, lifestyle also influences the PAI-1 concentration. Body mass reduction, physical activity and decreased insulin resistance lower its concentration. Pharmacologically induced decrease in PAI-1 concentration was observed with the administration of ACE inhibitors and angiotensin receptor blockers. Metformin and thiaizolidinediones also decreased PAI-1 activity [64,66,67].

CONCLUSIONS

The adipose tissue-derived cytokines play an active role in the metabolism in obese and overweight subjects. There are significant adverse associations of adipocytokines and inflammatory markers with multiple complications of obesity. In practice, the primary aim of the rational therapeutic strategy is to reduce the amount of adipose tissue and thus prevent metabolic disturbances.

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