ADIPOSE TISSUE HORMONES AND APPETITE AND BODY WEIGHT REGULATORS IN INSULIN RESISTANCE

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ABSTRACT
Impaired sensitivity to insulin (the so called insulin resistance, IR) occurs in a number of genetic and acquired conditions, including obesity, non-insulin dependent diabetes mellitus, polycystic ovary syndrome (PCOS) and metabolic syndrome (MS). In this review we discuss the correlation between IR, the adipose tissue hormones and appetite and body weight regulators. Leptin acts as a major adipostat: it suppresses food intake and activates catabolic pathways associated with increased energy production. It improves the peripheral insulin sensitivity and affects β-cell function. Adiponectin is the only adipocytokine discovered so far that has anti-atherogenic properties. There is a reverse correlation between the serum adiponectin levels and the degree of obesity, IR, impaired glucose tolerance, dyslipidemia and atherosclerosis. Ghrelin stimulates food intake; of all circulating orexigenic hormones ghrelin is the most thoroughly studied. Ghrelin levels are decreased in MS and PCOS patients as this hormone is negatively correlated with body mass. Resistin is a hormone secreted by adipose tissues; a growing body of evidence suggests that it might be implicated in the link between obesity and diabetes. It has been found that the hormone's levels are significantly higher in obese people than those in normal body mass people. The recently discovered adipose tissue hormones, vaspin, visfatin, omentin-1 and their effect on IR development, have been increasingly researched.

Key words: insulin resistance, adipose tissue, obesity, metabolic syndrome

INTRODUCTION
Obesity is a major health problem worldwide. Obesity and overweight rates are increasing dramatically, which surely leads to an increased risk of developing cardiovascular diseases (CVD) and cerebrovascular disorders, type 2 diabetes, joint and respiratory disorders, and cancer. Adipose tissue has been shown by the recent advances in science to be an active endocrine organ that synthesizes and releases a number of bioactive mediators (adipocytokines) that are involved in the maintenance of the homeostasis, blood pressure control, the lipid and carbohydrate metabolism and in the development of low-grade inflammation and atherosclerosis. The effect of adipocytokines and appetite regulators on the processes of development of insulin resistance (IR) is a subject of intense research interest. It has been found that plasma levels of the cytokines resistin, leptin, TNF-α, interleukin-6 (IL-6), C-reactive protein, fibrinogen and plasminogen activator inhibitor - 1 and others, tend to be elevated in patients with obesity and diabetes.¹² There is evidence that the subcutaneous adipose tissue, composed of small insulin-sensitive adipocytes, functions as an energy storage and lacks visceral stroma and cellular infiltration. The visceral adipose tissue contains large insulin-resistant adipocytes; it has a well-developed vascular system and is characterized by infiltration of a large number of inflammatory cells. Android obesity is characterized by a reduction of adiponectin whose main effect is increasing insulin sensitivity.¹² It is believed that at an equal degree of overweight, people with more visceral fat are at a greater risk of developing cardiovascular diseases. Gender and ethnicity are related to the distribution of adipose tissue and fat metabolism.³
INSULIN RESISTANCE - NATURE AND CAUSES

The American Diabetes Association defines insulin resistance (IR) as an impaired metabolic response to either exogenous or endogenous insulin. Other authors define it as a condition in which the target cells cannot respond to the ordinary levels of circulating insulin. Although what mechanisms exactly lead to IR in a specific tissue are still unclear, it is basically thought that the condition is due to pre-receptor or post-receptor abnormalities.4

Insulin is an anabolic hormone involved in the metabolic control, energy balance and the maintenance of normal body mass by acting on key tissues such as skeletal muscles, liver, and adipose tissues. Many physiological conditions and circulating factors can affect the insulin action. Glucocorticoids, glucagon, catecholamines, the growth hormone and prolactin can induce IR in cases of excessive secretion separately (in specific endocrinopathies) and combined effects (as in stress or infection). IR can also develop in a number of genetic and acquired conditions, including obesity, non-insulin-dependent diabetes, PCOS and MS.5 With the exception of some rare cases in which antibodies to the insulin receptor or mutations of the gene for insulin receptor are found, IR in MS is caused by disorders affecting processes distally from binding of insulin to its receptor.6 (Table 1).

Hyperinsulinemia and the reduced insulin sensitivity are normally associated with lipid disorders (increased VLDL, IDL, and LDL and low HDL levels, elevated triglycerides (TG) levels, high relative concentration of small dense LDL particles - phenotype B), which are well known risk factors for coronary heart disease and other cardiovascular complications. High TG and low HDL cholesterol levels are associated with a 4.4-times higher risk of CVD, and the combination of hyperinsulinemia, increased apo-B and the presence of small, dense LDL-particles leads to an almost 5-fold increase of the risk.7 IR underlies several disorders of coagulation and fibrinolysis and the adverse changes associated with them within the vessel wall which increase the cardiovascular risk.

The insulin resistance in fatty tissues is considered an early and irreversible disorder, which can account for its relation to adipocyte dysfunction and peripheral tissues disorders. It has been demonstrated by lots of studies that systemic inflammation, IR in skeletal muscles and liver, hypertension, dyslipidemia and hyperglycemia are reversible if body weight is reduced, while IR and hypoperfusion in adipose tissues remain unaffected.9 This is confirmed by the fact that the defects associated with the movement of glucose transporters (GLUT4) to the cell membrane have a reversal progress in the myocytes but not in the adipocytes.

ADIPOSE TISSUE HORMONES AND REGULATORS OF APPETITE AND BODY WEIGHT AND THEIR RELATIONSHIP WITH THE INSULIN RESISTANCE

Adipose tissues secrete numerous substances that perform various functions (Table 2). These substances include free fatty acids (FFA): these have well-described pathophysiological effects on carbohydrate homeostasis, and proteins (adipocytokines): these act locally or systemically altering the insulin sensitivity of the target organs (muscle, liver),

<table>
<thead>
<tr>
<th>Table 1. Causes for insulin resistance</th>
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<td><strong>Internal (primary) defects in target cells</strong></td>
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<td>- Mutations in the insulin receptor gene (leprechaunism, Rabson-Mendenhall syndrome, type A insulin resistance syndrome);</td>
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<td>- Mutations in insulin receptor substrate-1;</td>
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<td>- Suspected defects in other signalling molecules, glucose transporters;</td>
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<td>- PC-1 (inhibitor of insulin receptor kinase activity)</td>
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<tr>
<td><strong>Secondary factors affecting the target cells</strong></td>
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<tr>
<td>- Pathological conditions - stress (inc. fever, sepsis), starvation, uremia, cirrhosis, ketoacidosis, obesity, diabetes or hyperglycemia;</td>
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<td>- Physiological conditions - puberty, advanced age, pregnancy;</td>
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<td>- Specific hormonal or metabolic factors - glucocorticoids (Cushing’s syndrome), growth hormone (acromegaly), hyperprolactinemia, catecholamines (pheochromocytoma), glucagon (glucagonoma syndrome), thyroid hormones (thyrotoxicosis), hyperinsulinemia (insulinoma), hyperglycemia (diabetes), non-esterified (free) fatty acids (lipodystrophy), adenosine, islet amyloid polypeptide (amylin);</td>
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<tr>
<td>- Antibodies against insulin receptor (type B insulin resistance syndrome)</td>
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their effects becoming manifest by neuroendocrine, autonomous and immune mechanisms. In addition, the stromal cells in adipose tissues are involved in the glucocorticoids and sex hormones metabolism, affecting the adipogenesis, carbohydrate and lipid metabolism and cardiovascular functions.9,10

Adipose tissues are an important source of inflammatory factors in obese patients with type 2 diabetes not only because of the various cytokines secreted by the adipocytes, but also because of the infiltration with pro-inflammatory macrophages. The macrophages in the adipose tissues are known to produce almost all TNF-α and significant part of IL-6.11

The level of expression of TNF-α from the adipose tissue in humans correlates positively with body mass index (BMI), percentage of body fat and hyperinsulinemia. It has been found that weight loss reduces the TNF-α levels.12 There is much evidence pointing at the role this cytokine plays in the quantitative regulation of fatty tissue – it inhibits the maturation of fatty cells; it promotes the insulin action – post-receptor defect followed by insulin resistance.13 Some researchers found that the insulin resistance changes with the changes in the TNF-α levels, while others found no correlation between the latter and insulin sensitivity, which fact requires further studies to elucidate it.14

The evidence suggesting that IL-6 contributes to the development of insulin resistance is also quite contradictory. Generally, the IL-6 circulating levels are elevated in obese patients with IR. It is suggested that the persistently high IL-6 levels in chronic inflammation (obesity and type 2 diabetes) can impair insulin sensitivity, while its periodically observed elevated levels are characterized by normal carbohydrate homeostasis.14,15

Leptin is a 16 kDa peptide hormone composed of 167 amino acids. Leptin exists in a free form and a receptor-bound form in the body where it performs the functions of a bioactive hormone. It is expressed in small amounts in various tissues such as stomach epithelium, placenta, muscle tissue, brain, but it is believed that it is predominantly produced and secreted by adipose tissues. It has been found that the plasma leptin levels are directly proportional to the amount of adipose tissue in the body; they decrease rapidly during fasting and increase postprandially.16 This regulation of leptin secretion is partially controlled by insulin. Leptin is important not only for the regulation of energy balance and food intake, but also functions as metabolic and neuroendocrine hormone: it is implicated in glucose metabolism and some reproductive processes, interacts with the hypothalamic-pituitary-adrenal axis, the thyroid gland and growth hormone, interferes even with the hematopoietic and immune systems.17 The leptin in the brain interacts with almost all neuropeptides that are involved in the regulation of energy balance and food intake. Thus leptin inhibits the secretion of neuropeptide Y (NPY). NPY is secreted by the hypothalamus and stimulates the appetite causing hyperphagia, accumulation of body fat, decreased thermogenesis and inhibition of sympathetic activity. Leptin levels elevates with meals and then it binds with its receptor in the hypothalamus, which stops the secretion of neuropeptide Y. There are scarce data

<table>
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<th>Adipokines</th>
<th>Effects</th>
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| TNF-α, IL-6 | - stimulate lipolysis and secretion of VLDL,  
|            | - decrease insulin sensitivity,  
|            | - suppress the expression of adiponectin. |
| Leptin     | - increases insulin sensitivity,  
|            | - increases hepatic TG secretion,  
|            | - in obesity                       |
| Lpinectin  | - indicative of risk of developing liver steatosis and diabetes;  
|            | - in insulin resistance.          |
| Resistin   | - decreases insulin sensitivity,  
|            | - increases hepatic TG secretion;  
|            | - in obesity and diabetes.        |
| Visfatin, vaspin, omentin-1 | - increase insulin sensitivity |

Table 2. Biological actions of major adipocytokines
on the changes in NPY levels in insulin resistance.\textsuperscript{8,9} The relationship between leptin and IR with all its consequences is a subject of intensive study and discussions. Current evidence suggests that circulating leptin is strongly correlated with insulin and fasting glucose, NOMA-index, dyslipidemia, hypertension, independently or only partially dependently on obesity.\textsuperscript{18} Leptin is thought of being a major adipostat – it suppresses food intake and activates catabolic pathways associated with increased energy production. Moreover, leptin improves peripheral (liver and skeletal muscle) insulin sensitivity and affects beta-cell function. With the exclusion of patients with intact leptin receptor and high circulating leptin levels, most obese patients do not lose body weight after exogenous administration of leptin. This diminished response of leptin to anorexigen and insulin sensitising factors is called leptin resistance.\textsuperscript{8,19}

The idea that leptin acts as an antiobesity hormone is based on the following observations: first, rodents and humans with a genetic deficiency in leptin or leptin receptors develop IR-associated insatiable appetite and morbid obesity, hyperlipidemia, and manifestation of diabetes; second – administration of leptin peripherally or intraventricularly in mice decreases food intake, body weight and body fat, in consistence with the notion of negative feedback regulation in the brain.\textsuperscript{8} It has become evident that leptin is the long sought hormone that links adipocyte metabolism and body weight via the appetite centres in specific hypothalamic areas of the brain. Treatment of leptin-deficient ob/ob mice with recombinant leptin stimulates the catabolic processes associated with increased energy production and ultimately, inhibits food intake, reduction of body weight and decrease of body fat as a whole.\textsuperscript{8,20}

It is interesting to note that the hyperglycemia and IR in ob/ob mice are affected at doses of leptin that do not cause weight loss. This shows that the effect leptin exerts on IR is independent of its effects on body weight. In the absence of obvious defects by the leptin receptor, a leptin therapy in humans and mice with ‘normal’ (diet-induced) obesity is characterized by a minimal effect on food intake inhibition and weight reduction. The blunt response to leptin, called leptin resistance underlies obesity, impaired insulin action, diabetes and elevated atherogenic lipids. Leptin resistance arises most likely from leptin transport reduction across the blood-brain barrier and impairment of the signal transduction of leptin in the brain.\textsuperscript{8,19}

Low leptin levels lead to suppression of thermo-genesis and decreased levels of growth hormone, thyroid and sex hormones. Furthermore, lower leptin during fasting is associated with the onset of immunosuppression, apathy and activation of the hypothalamic-pituitary-adrenal axis in rodents. These changes, induced by starvation and consequently by low levels of leptin, mimic the metabolic phenotype of congenital leptin deficiency in Lep db/db mice. Leptin deficiency is regarded as a state of starvation in which some adaptation mechanisms such as hyperphagia, reduced base exchange and changes in hormones are triggered aiming at restoring the energy balance.\textsuperscript{8} Leptin treatment prevents the suppression of the reproductive axis, thyroid function, growth hormone and energy expenditure, and the hyperphagia usually observed in fasting or prolonged weight reduction. The congenital leptin deficiency is associated with expression of hypothalamic hypogonadism and lack of pubertal development. Women with hypothalamic amenorrhea have low levels of leptin associated with blunt luteinizing hormone pulsatility.\textsuperscript{19}

Adiponectin (also known as AcrP30, adipocyte complement-related protein 30 kDa or AdipoQ) is a 247-amino acid peptide secreted primarily from adipose tissue. It was identified as an adipocyte-derived hormone almost simultaneously by four teams in the 1990s of the 20\textsuperscript{th} century, but remained in obscurity until the early twenty-first century. It is a model (prototype) of anti-inflammatory adipocytokine. There is a reverse correlation between serum adiponectin levels and the degree of obesity, IR, impaired glucose tolerance, dyslipidemia and atherosclerosis.\textsuperscript{8,21} Accumulation of visceral fat results in hypoadiponectinemia because adiponectin expression is downregulated in the tissue. This inhibits the insulin action in the liver, muscles and other peripheral tissues. High levels of adiponectin are an independent factor for increased insulin sensitivity and reduced risk of type 2 diabetes. Adiponectin has a beneficial effect on glucose and lipid metabolism. In case-control studies, low plasma levels of adiponectin were shown to be a risk factor for future development of type 2 diabetes, but not of obesity.\textsuperscript{21} Evidence that adiponectin has a key role to play in developing insulin resistance has been provided by some genetic studies identifying the type 2 diabetes and metabolic syndrome loci in chromosome 3q27 where actually the adiponectin production coding gene is located. The mechanisms whereby adiponectin reduces IR are not fully understood. It has been suggested that these mecha-
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Ghrelin is secreted from the fundic region of the stomach and has been identified as the endogenous ligand for the growth hormone secretagogue receptor. Fasting increases plasma ghrelin, and exogenous ghrelin increases food intake when administered peripherally or centrally. It is noteworthy that ghrelin levels rise shortly before scheduled meals and fall shortly after meals end. Ghrelin levels have been found to be low in MS and PCOS patients as expected in consistence with the existent negative correlation between ghrelin and body weight. Ghrelin concentration is low in patients with type 1 and type 2 diabetes, with the postprandial response weak or similar to that of healthy individuals. Patients with obesity, IR and hyperinsulinemia have low levels of ghrelin. This appetite regulator features a variety of functions and any disruption of its secretion may cause hyper- or hypophagia, may result in obesity and development of MS, growth retardation, cardiovascular events, and adverse affection of some reproductive processes. The ghrelin/leptin ratio has been recently studied as a potential atherogenic marker.

Vaspin is visceral adipose tissue-derived serine protease inhibitor that reduces serum leptin, resistin and TNF-α and elevates adiponectin levels and improves insulin sensitivity. Vaspin DNA was isolated for the first time in visceral white adipose tissue of rats that are used as an animal model of type 2 diabetes with visceral obesity. Human vaspin is a protein composed of 395 amino acids; it has approximately 40% homology with α1-antitrypsin. Its concentrations are low in lean subjects and elevated in overweight patients, especially if their glucose tolerance has been impaired. Vaspin expression decreases with worsening of diabetes and body weight loss. Serum vaspin, as shown in some studies, reaches peak values before meals and at night, while postprandially its concentration drops abruptly. Meal-related changes in serum vaspin concentrations suggest that vaspin has a role in the regulation of nutrient and body weight homeostasis. Administration of recombinant vaspin to a mouse model of diet-induced obesity improved glucose tolerance and insulin sensitivity. Higher plasma concentrations of vaspin have been found in men with MS. Tan et al. reported for the first time elevated serum and fatty tissue vaspin levels in overweight women with PCOS. They demonstrated that metformin therapy can lower serum vaspin concentrations.

A novel adipose-tissue-derived protein termed visfatin has been described with putative antidiabetic properties. Visfatin was originally isolated as a cytokine that enhances the maturation of B-cell precursors and termed accordingly a pre-B cell colony enhancing factor (PBEF). Intracellularly visfatin/PBEF functions as an enzyme, nicotinamide phosphoribosyltransferase, that catalyzes the oxidation of nicotinamide riboside to nicotinamide ribosyladenosine, and elevates adiponectin levels.

Visfatin/PBEF functions as an enzyme, nicotinamide phosphoribosyltransferase, that catalyzes the oxidation of nicotinamide riboside to nicotinamide ribosyladenosine, and elevates adiponectin levels. Adiponectin also directly stimulates glucose uptake in adipocytes and muscle by activating AMP-activated protein kinase. In addition to its effects on fuel homeostasis, adiponectin may have anti-inflammatory properties. It inhibits myelomonocytic and phagocytic activity, and the TNF-α production by macrophages. Because of its effects on insulin sensitivity and inflammation process, adiponectin is regarded as an anti-atherogenic factor. It has been shown that adiponectin knockout mice have high levels of TNF-α, increased insulin resistance and susceptibility to atherosclerosis. Lower adiponectin is also associated with increased production of proinflammatory proteins IL-6 and C-reactive protein. The low levels of adiponectin have been found to be strongly correlated with coronary artery disease.

Resistin is a member of a class of cysteine-rich proteins collectively termed resistin-like molecules. It is produced and secreted mainly by peripheral blood mononuclear cells. This recently discovered fat tissue hormone is thought to represent a link between obesity and diabetes. Data about its circulating levels and physiological role are rather scanty and controversial. Some researchers found the resistin levels in obese patients to be significantly higher than those in normal weight patients, while others found no significant differences. Contradiction exists also in the data concerning statistically significant correlations between the levels of resistin, weight, adipose tissues, IR, and these in combination in basal conditions and after weight loss. Secretion of resistin is beneficially affected by the proinflammatory cytokines TNF-α and IL-6. Resistin has been found to induce the expression of TNF-α and IL-6 in white adipose tissue and peripheral mononuclear cells.

Ghrelin, a peptide hormone, is a product of specific endocrine cells in the stomach and duodenum. It stimulates food intake and is considered to be the most thoroughly studied circulating orexigen. Ghrelin is secreted from the fundic region of the stomach and has been identified as the endogenous ligand for the growth hormone secretagogue receptor. Fasting increases plasma ghrelin, and exogenous ghrelin increases food intake when administered peripherally or centrally. It is noteworthy that
formation of nicotinamide adenine dinucleotide. Thus it inhibits the apoptosis and is involved in fuel metabolism during stress and immune involvement. The visfatin production gene is isolated mainly in the visceral fat. Visfatin stimulates the glucose uptake by adipocytes and myocytes and suppresses glucose release from liver cells. Fukuhara et al. describe visfatin as an adipokine that lowers plasma glucose and is able to bind to the insulin receptor and activate it by triggering the tyrosine phosphorylation cascade. Visfatin acts as insulin mimetic which partially affects (reduces) IR despite circulating in much lower concentrations than those of insulin.\textsuperscript{29} Visfatin is involved in the formation of adipocytes. The overexpression of its production gene in pre-adipocytes boosts their differentiation into mature adipocytes and stimulates the process of fat accumulation in the cells. Several studies have shown that plasma visfatin levels correlate highly with obesity, visceral fat mass, type 2 diabetes and MS. Visfatin concentrations are high in MS patients, those that are overweight and obese, have greater waist to hip ratio, high blood pressure, high fasting plasma glucose levels, serum TG and low HDL-cholesterol.\textsuperscript{23}

Omentin (intelectin) is synthesized by the visceral stromal vascular cells in the omentum (but not by adipocyte). It is suggested that it improves insulin sensitivity by stimulating the insulin dependent glucose transport in human subcutaneous adipose tissue and visceral adipose tissue. It plays a key role in the pathogenesis of obesity and comorbid diseases.\textsuperscript{23} Levels of omentin-1 (the principal circulating isoform in plasma) decrease in obesity and IR and increase with the increase of serum concentrations of HDL-cholesterol and adiponectin. Plasma omentin levels are inversely correlated with BMI, waist circumference (cm) and leptin concentrations. Omentin-1 is decreased in patients with acute coronary syndrome and stable angina pectoris. Its serum concentrations are significantly lower in patients with type 2 diabetes and impaired glucose tolerance, women having relatively higher levels of serum omentin than men.\textsuperscript{23,30} Serum adiponectin levels have been found to change similarly to the way omentin levels change in these conditions. This suggests a close relationship between these two adipokines. Serum omentin-1 levels in women with PCOS are significantly lower than those in healthy women. A 6-month treatment with metformin was found to increase omentin-1.\textsuperscript{31}

**CONCLUSIONS**

There have been a great deal of research in recent years on the role of adipocytes in the mechanisms of development of insulin resistance. Adipose tissue is now considered an active endocrine organ secreting a great number of adipocytokines which may have a direct effect on the immune system. A growing body of evidence suggests that there is a chronic low-grade inflammation in obesity and related metabolic disorders, such as IR, type 2 diabetes, hypertension and dyslipidemia, MS. The relationships between IR and adipose tissue-derived hormones are attracting a stronger scientific interest now so that reliable prognostic markers and novel therapeutic approaches to combat obesity and several metabolic complications could be developed.

**REFERENCES**

11. Fernández-Real JM, Pickup JC. Innate immunity,
Гормоны жировой ткани и регуляторы аппетита и массы тела при инсулиновой резистентности

Д. Колева, М. Орбецова, П. Атанасова

Резюме
Нарушена чувствительность к действию инсулина или панкреатического инсулинового синдрома (ИР) наблюдается при ряде генетических и приобретенных заболеваний, включающих ожирение, неинсулинозависимый сахарный диабет, поликистозный овариальный синдром (PCOS) и метаболический синдром (МС).

В настоящем обзоре рассматривается связь между ИР, гормонами жировой ткани и регуляторами аппетита и массы тела. Лептин действует как основной “адипостат” — подавляет прием пищи и приводит к активации катаболических путей, связанных с повышенным производством энергии. Лептин улучшает периферическую инсулиновую чувствительность и оказывает влияние на β-клеточную функцию. Адипонектин, резистин, оментин, систолический и диуретический индексы также связывают с ИР, влияя на инсулиновый метаболизм, а оментин и лептин активируют и подавляют адипонектин в зависимости от уровня ИР.

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кулающий орексисан. Уровни греция уменьшены у пациентов с МС и PCOS в соответствии с отрицательной связью между греция и массой тела. Резистин - это гормон жировой ткани, о котором имеются накопленные доказательства, что существует связь между ожирением и диабетом. Установлены сиинфикационно более высокие уровни резистина среди лиц с ожирением по сравнению с лицами с нормальной массой тела.

Наблюдается увеличенный научно-исследовательский интерес к изучению новых гормонов жировой ткани (васпин, висфатин, оментин-1) и к их влиянию на развитие ИР.