Adipokines and cardiometabolic syndrome

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Abstract

Obesity is one of the most important public health challenges of the XXI century. Currently, the adipose tissue is considered as an active endocrine organ producing hormones — adipokines. Adipokines are the regulators of insulin sensitivity, oxidative stress, energy metabolism, coagulation and inflammatory reactions. That's why adipokines may be retailers of mechanism of negative actions of obesity on the cardiovascular system. The study of their pathophysiological role will unveil the potential of adipokines as a therapeutic target in the treatment of obesity and associated conditions.

Key words: adipokines, adipose tissue, obesity.

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Резюме

Ожирение является одной из наиболее важных проблем общественного здравоохранения XXI века. В настоящее время жировая ткань рассматривается как активный эндокринный орган, производящий гормоны — адипокины. Адипокины являются одними из регуляторов чувствительности к инсулину, оксидативного стресса, энергетического обмена, свертываемости крови и воспалительных реакций. Именно поэтому адипокины могут являться реализаторами механизма негативного действия ожирения на сердечно-сосудистую систему. Изучение их патофизиологической роли может сделать адипокины терапевтической мишенью в борьбе с ожирением и ассоциированных с ним состояний.

Ключевые слова: адипокины, жировая ткань, ожирение.

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Introduction

Obesity is one of the most important public health problems in the XXI century. There are 1.6 billion overweight adults in the world, and about 400 million of them are obese. Overweight and obesity are closely connected with cardiovascular diseases, type 2 diabetes mellitus (DM), diseases of the musculoskeletal system, some types of cancer. Due to this studies of obesity mechanisms, pathophysiological properties and laws of this process are an important and urgent task for researchers worldwide.

Metabolic syndrome (MS) — a combination of the most important cardiovascular risk factors — can be found in most cardiologist patients. MS is associated with the 5-fold increase in the risk of type 2 DM and 2-fold increase in the risk of cardiovascular disease (CVD) in the next 5–10 years [1] (MS patients have 2–4-fold risk of stroke, and 3–4-fold risk of myocardial infarction compared to those without MS) [2]. Abdominal obesity is the most common component of MS. Adipose tissue, including abdominal fat, is a heterogeneous mixture of adipocytes, stromal pre-adipocytes, immune cells, endothelium, and adipocyte hyperplasia and hypertrophy quickly develops in response to an excessive food intake [3]. Currently, the understanding that adipose tissue is a storage of fatty acids and energy has been replaced by the concept of adipose tissue as an active endocrine organ producing hormones — adipokines (originally called «adipocytokines») that are biologically active low molecular weight proteins. Visceral fat has the highest metabolic activity, and according to a recent study is the only significant predictor of insulin resistance [4]. Adipokines are regulators of insulin sensitivity [5], oxidative stress [6], energy metabolism, blood clotting and inflammatory reactions [7].

Increase in visceral fat mass and adipocyte hypertrophy leads to fat cells perfusion problems and hypoxia [8]. In response to ischemia necrosis and macrophages infiltration develop in adipose tissue, resulting in the excessive synthesis of proinflammatory cytokines and adipokines, free fatty acids, tumor necrosis factor alpha, interleukin-6, plasminogen activator inhibitor-1 (PAI-1), C-reactive protein (CRP) [9]. As a result, chronic inflammation is maintained in adipose tissue, which leads to the systemic inflammation and obesity-associated diseases and pathological states such as endothelial dysfunction, and atherosclerosis [10]. In patients with overweight and obesity, there is a dysregulation of adipokine secretion — some of them are reduced while other are increased.

In recent years, the attention of researchers was focused on the role of some adipokines in the CVD development, as well as their relationships with each other and MS components. Negative effects of MS components on the cardiovascular system can be realized through adipokines, so we can hypothesize that finding novel adipokines will contribute the changes in treatment strategy of metabolic disorders.

Adiponectin and leptin are the most well-studied adipokines. After the discovery of leptin in 1994 adipose tissue has been considered an endocrine organ. Other adipokines are actively studied nowadays including visfatin, plasminogen activator inhibitor-1, resistin, and ghrelin. Ghrelin is a peptide hormone synthesized primarily in the stomach, small and large intestine. It is not an adipokine, but it has metabolic functions.

This review highlights the role of some adipokines, including ghrelin, in the formation of conditions associated with obesity.

Adipokines and obesity

Adiponectin is a hormone of adipose tissue that was opened in 1995. Adiponectin with high molecular weight (high molecular weight oligomer) in contrast to the other two isomers, is regarded as the active form of the adipokine [11] and is the most important marker for the assessment and monitoring of treatment of patients with MS and concomitant disorders. Reduction of high molecular weight oligomer adiponectin is predictive of MS progression. Lifestyle modification, body mass index (BMI) and waist circumference (WC) reduction lead to an increase in the level of the high-mass adiponectin, while the levels of total adiponectin may not change [11, 12]. Adiponectin is inversely correlated with BMI and the amount of visceral fat [13].

Leptin was the first discovered adipokine (1994) and was called «hunger hormone» due to its role in the regulation of satiety and energy consumption [14], as well as in the control of appetite. There are six leptin isoforms different in their biological actions [15]. In the hypothalamus, leptin decreases oreksigenic and increases anorexigenic peptide synthesis by inhibition of adenosine monophosphate (AMP)-activated protein kinase in the arcuate nucleus and activation of acetyl-CoA carboxylase. As a consequence, an increase in leptin level leads to appetite reduction [16]. Thus, a transient increase in

leptin levels occurs during meal, and fasting leads to its decrease. Most overweight and obese patients have elevated blood leptin levels, however, the appetite suppression is not observed, i. e. there is a resistance to leptin. Leptin resistance is considered to be one of the fundamental pathophysiological components in obesity [17]. Hereditary leptin deficiency leads to severe obesity, hyperphagia, and reproductive dysfunction. Plasma leptin concentration is proportional to the amount of adipose tissue in the body [18]. Leptin level increases exponentially with BMI and is considered an independent risk factor for obesity [19].

Ghrelin, discovered in 1999, like leptin, is involved in the regulation of food intake and energy homeostasis. However, there is an inverse relationship between ghrelin and leptin — fasting increases ghrelin level and food intake leads to its decrease [20]. Its concentration in blood decreases with the higher BMI, WC and obesity [21, 22] and increases with weight loss. Ghrelin promotes weight gain by increasing appetite and food consumption while reducing energy expenditure. It acts in the hypothalamus, stimulating arcuate nerve activity and thus reproduces the effects of neuropeptide Y in the paraventricular nucleus of the hypothalamus [23]. Factors involved in the regulation of ghrelin secretion are not yet fully identified. Interestingly, exogenous administration of somatostatin and its analogs reduces circulating ghrelin level, while leptin administration does not alter ghrelin level in the blood.

In 2001, a new adipokine, resistin, was discovered. Its plasma concentration positively correlates with BMI and WC, circulating levels of resistin increase with age, probably reflecting the increase of adipose tissue [24]. In mice, resistin is secreted mainly by white adipose tissue, however, in humans it is mostly produced by macrophages [25]. Obese people have high macrophage infiltration in adipose tissue, and, as a consequence, a high level of resistin in adipose tissue samples, as well as elevated levels of circulating resistin compared to lean people [26]. Weight loss by means of a diet or bariatric surgery lead to the reduction of resistin level. At the same time, some studies did not show a link between resistin and obesity [27], but the results of the cross-sectional Framingham study showed correlation between resistin level and the amount of visceral fat [28].

Another adipokine — visfatin — was opened in 2005. The term «visfatin» comes from the phrase «visceral fat», since it was assumed that visfatin concentration is much higher in visceral fat than in subcutaneous fat. However, following studies showed comparable visfatin concentration in the subcutaneous and visceral fat [29]. This hormone is released not only by adipocytes, but also by activated macrophages, infiltrating adipose tissue in obesity [30]. Numerous studies have shown contradictory data on the circulating visfatin concentration in obese patients: in some studies, the level was raised, in others it was comparable to the control group, while some authors reported even reduced visfatin level [31–34]. So far, it is not clear exactly how visfatin is associated with obesity.

The circulating level of plasminogen activator inhibitor-1 is increased in obesity [35] and PAI-1 is independently associated with central fat distribution [36]. Animal studies confirmed pathogenetic role of PAI-1 in the development of obesity and insulin resistance. Thus, in a mice model of obesity, induced by high fat- or high carbohydrate diet, PAI-1 gene deficiency (PAI-1 gene -/-) prevented obesity and insulin resistance. At the same time, mice with genetically determined obesity and diabetes lacking PAI-1 gene, had lower weight, fat content, as well as lower glucose and insulin levels compared to individuals with PAI-1 gene [37, 38].

Adipokines and carbohydrate metabolism

Adiponectin suppresses hepatic enzymes, involved in gluconeogenesis, reduces the speed of endogenous glucose production in the liver, which increases the transport of glucose into muscle and increases fatty acid oxidation [39], and improves the sensitivity of tissues to insulin. In pregnant women with gestational diabetes onset adiponectin level was significantly lower than that in women with euglycemia, so adiponectin level might be used as an early marker of gestational diabetes in this group [40].

High leptin level in obesity is associated with hyperinsulinemia and insulin resistance [41]. However, relationship between increased leptin level and type 2 DM is still not clear. In a recent small study of 65 patients with type 2 DM, there was no significant difference in leptin level between non-obese patients with and without type 2 DM. High levels of leptin were largely associated with obesity than with type 2 DM [42].

There is an inverse relationship between the level of circulating insulin and ghrelin in humans [21]. Ghrelin level decreases after glucose load (100 g) along with the increase in insulin level (insulin-induced

hypoglycemia, 0.1 IU/kg insulin intravenously). The studies indicated a biphasic response to ghrelin administration: at first, insulin synthesis is inhibited, then its secretion is stimulated [43, 44]. Further studies are needed to clarify such variability in insulin homeostasis and thus glucose in response to ghrelin. Ghrelin level inversely correlates with the index of insulin resistance [22].

Initially, it was suggested that resistin links obesity with diabetes [45]. However, in contrast to the experimental results in mice, no significant differences in resistin level were found between patients with or without insulin resistance, and patients with or without type 2 DM. Nevertheless, resistin levels are increased in hypercaloric diet-induced obesity and genetic models of obesity and insulin resistance. Insulin resistance levels positively correlate with resistin expression [46]. The highest concentration of resistin was found in abdominal fat in obese patients [47], and increase in abdominal fat is the major risk factor for insulin resistance. Studies of human resistin application in mice showed that human resistin causes inflammation occurrence in visceral fat and insulin resistance. This demonstrates that resistin may be a link between inflammation and glucose homeostasis [48]. Also in 10-year prospective studies elevated basal level of resistin was associated with significantly higher risk of type 2 DM, even after adjusting for other risk factors [49, 50].

Visfatin has been previously considered as an adipokine with insulin-like properties [51]. Binding to insulin receptors in mice cell cultures, visfatin led to the reduction of blood glucose level by stimulating glucose uptake in cell culture and fat accumulation in the pre-adipocytes. Later, however, the authors had o disclaim this statement due to the inability to reproduce hypoglycemic properties of visfatin [52]. However, subsequent studies have shown that visfatin can increase insulin secretion, and can directly activate insulin receptors of the beta-cells stimulating phosphorylation [53]. A recent study showed that visfatin stimulates beta-cell proliferation in a MIN6 cell line and inhibits cell apoptosis [54].

Cross-sectional studies have shown an association of PAI-1 with proinsulin and fasting insulin levels [55]. In a study of 843 people, with a follow-up of 5.2 years, the contribution of PAI-1 in the development of insulin resistance and DM was studied. It was shown that high basal level of PAI-1 and its elevation over time were associated with the development of insulin resistance and type 2 DM. It was detected regardless of the common risk factors for type 2 DM. In patients without DM and in healthy people PAI-1 progression was associated with impaired glucose tolerance and subsequent DM onset, even when adjusted for demographic data, smoking and basal level of PAI-1 [56]. Another large study also showed a relationship of insulin resistance with PAI-1 level, even when adjusted for obesity [36]. Based on these data, the authors suggested a negative indirect effect of hyperglycemia, insulin resistance and obesity on the development of endothelial dysfunction as a result of violations of fibrinolysis and systemic inflammation. PAI-1 was a marker of both of them.

Adipokines and hypertension

There is a number of hypothetical pathogenic mechanisms, connecting obesity and high blood pressure (BP) (hypertension) [57]. These include activation of the sympathetic nervous system, renin-angiotensin-aldosterone system, metabolic disorders (including hyperinsulinemia, adipokine imbalance, increasing number of cytokines). Influence of adipokines in overweight and obesity is probably one of the key processes in the development of hypertension. Both the influence of individual adipokines, the most significant of which is leptin, and the overall effect of the adipokines imbalance, maintenance of oxidative stress and inflammation leading to endothelial dysfunction are important. Reducing the concentration of nitrogen oxide impairs vascular relaxation, which leads to vasoconstriction in hypertension. Also influenced by some adipokines, including leptin, vascular stiffness increases, which also leads to an increase in BP.

According to some studies, adiponectin correlated inversely with BP level [58], according to the other — there was no independent association between adiponectin and BP [59]. The overweight effects might mediate this relationship. At the same time, some studies show an inverse relationship between adiponectin and arterial stiffness indicators [60].

Leptin exerts its effect through the hypothalamus, increasing BP by activating the sympathetic nervous system [61]. High levels of circulating leptin in obese people are associated with an increase in sympathetic tone of the renal arteries [62]. Leptin is a NO-dependent vasodilator, it also increases vascular resistance due to smooth muscle cell proliferation and activity of the sympathetic nervous system [63]. Leptin was shown to be associated with

an increase in systolic, diastolic, and pulse BP. It is noteworthy that the relationship between leptin and BP was stronger in men [59]. In a study of 294 healthy adolescents circulating leptin was significantly associated with an increase in arterial stiffness. Moreover, this association was independent of fat mass, BP, CRP or cholesterol level [64]. In addition, a direct link was found between leptin and arterial stiffness parameters in the study including 60 women [60].

Data on the relationship between ghrelin and BP pressure are contradictory. Ghrelin was shown to decrease the activity of sympathetic nervous system in rabbits [65]. Intravenous injection of ghrelin leads not only to the reduction in BP, but also to the increase in cardiac output in humans [66]. Also, another study showed that administration of ghrelin reduces BP equally in obese and lean people. It has recently been found, that acetylated ghrelin positively correlates with systolic BP and left ventricular myocardial mass in patients with MS, even after adjustment for BMI [67]. In a population study involving 1,037 people a link between ghrelin and office BP was found, but after adjustment for sex, age and BMI this association was not anymore significant. Home BP measurements also showed no relation to the level of ghrelin, but left ventricular hypertrophy was associated with increased ghrelin levels, also after adjustment for sex, age, BMI, and systolic BP [68].

Nowadays there is a very scarce and conflicting data on the direct effect of visfatin on vascular tone regulation. Basically they show that visfatin is associated with the impairment of endothelium-dependent vascular relaxation [69].

In a 14-year follow-up of 872 women without hypertension and DM elevated level of plasma resistin was independently associated with the higher risk of hypertension [70].

A multivariate analysis has shown an association between PAI-1 and every MS component, including hypertension [71]. The level of PAI-1 correlated with an increase in diastolic BP, and this association is detected both in hypertension and «prehypertension» [72]. Interestingly, the angiotensin receptor blockers reduce circulating levels of PAI-1 proportionally to the decrease in BP [73]. In a large Korean study of 1,312 women there was an association between locus polymorphism in PAI-1 gene and hypertension development: patients with PAI-1 4 G allele had more severe hypertension independently of age, BMI, cholesterol and glucose levels [74].

Adipokines and atherosclerosis

Previous studies have shown that adiponectin can prevent atherosclerosis, thereby suggesting its protective role against cardiovascular disease in patients with the MS and DM. Adiponectin demonstrates antiatherogenic multifactorial effects, including inhibition of endothelial activation, decline of macrophage conversion into foam cells and inhibition of smooth muscle cell proliferation [75]. There is an inverse correlation between adiponectin and low density lipoproteins, and serum triglyceride levels [58], and a direct association with high density lipoprotein level [76, 77]. The level of adiponectin is significantly lower in patients with coronary heart disease (CHD), and it may be an independent predictor of CHD [78]. At the same time, a recent meta-analysis of 16 prospective studies involving 14,063 patients with cardiovascular disease showed that elevated levels of adiponectin are associated with increased risk of death from all causes and cardiovascular mortality in patients with cardiovascular disease [79]. Among patients with the highest tertile levels of adiponectin all-cause mortality was 46 % higher, and mortality from cardiovascular causes — 69 % higher compared to the lowest tertile. The authors suggest that a a compensatory mechanism or adiponectine resistance might lead to adiponectin increase in patients with arterial lesions; besides compensation may not be optimal in advanced cardiovascular diseases, and adiponectin protective properties are no longer present. Further studies are needed to clarify the underlying mechanisms.

Leptin is a pro-atherogenic agent. It regulates NO-synthase activity in endothelial cells, and promotes the accumulation of reactive oxygen species [80], which stimulates proliferation and migration of endothelial and smooth muscle cells [81, 82]. Leptin facilitates the accumulation of cholesterol in macrophages [83] and stimulates angiogenesis [84]. Leptin positively correlates with plasma levels of CRP, PAI-1 [85]. Furthermore, it activates platelet aggregation and may contribute to arterial thrombosis [86].

Ghrelin is able to improve endothelial function in patients with MS, increasing the biological activity of nitric oxide [87]. Ghrelin inhibits the production of proinflammatory cytokines in human endothelial cells in vitro, as well as endotoxin-induced cytokine production in vivo. These anti-inflammatory effects of ghrelin may play a regulatory role in the development of atherosclerosis, especially in obese patients who demonstrated a reduced ghrelin level [88].

Resistin correlates with inflammation markers and may be a predictor of coronary artery atherosclerosis [93]. It induces expression of adhesion molecules in endothelial cells [89], and contributes to the formation of foam cells [90]. In one study, obesity and CRP were associated with increased levels of resistin in men with acute myocardial infarction [91]. Serum resistin levels are positively correlated with vascular inflammation leading to the development of atherosclerosis, that was confirmed by positron emission tomography with fluoro-18F-deoxyglucose [92]. In a cross-sectional SIRCA study of 879 asymptomatic patients, the association of coronary artery calcification with markers of inflammation and other risk factors was studied; Reilly at al. showed that elevated level of resistin is a predictor of coronary atherosclerosis, independent of CRP [93]. Resistin level correlated with the severity of coronary atherosclerosis in patients who underwent coronary angiography [94, 95]. Furthermore, resistin is a predictor of restenosis after coronary stenting and is an independent predictor of serious cardiovascular events in patients with coronary heart disease [96–98]. Based on a large-scale population-based study involving 6636 people, resistin was suggested to be a marker of coronary artery disease. Moreover, women have higher resistin levels. The group of nondiabetic patients with the highest resistin levels had higher risk of myocardial infarction, and it was higher in women than in men [99].

Circulating levels of visfatin positively correlate with the level of pro-inflammatory markers such as IL-6 and CRP. In recent years, visfatin was suggested as a marker of endothelial dysfunction and atherosclerosis [100]. Patients with cerebral atherosclerosis have significantly higher level of visfatin, so it may be an independent risk factor for stroke [101]. There is a positive relationship between visfatin level, atherosclerotic coronary artery disease and the presence of unstable plaques in patients with coronary artery disease and acute myocardial infarction [102]. High concentrations of visfatin were found in unstable foam cells of atherosclerotic plaques in patients with myocardial infarction. Thus, it was suggested that visfatin may be involved in the process of destabilization of plaques [102]. Visfatin also directly promotes proliferation of smooth muscle cells, contributing to the progression of atherosclerosis. Visfatin promotes angiogenesis by stimulating the migration and proliferation of endothelial cells and forming the capillaries [103, 104]. Abnormal angiogenesis is believed to contribute atherosclerotic lesions in carotid and coronary arteries [105]. In addition, visfatin can act indirectly by modulating the immune cells [106], in particular monocytes, promoting the synthesis and release of proinflammatory cytokines [102]. Thus, visfatin is a novel promising pharmacological target for the prevention and treatment of atherosclerosis.

PAI-1 is a marker of fibrinolysis and risk factor for atherothrombotic events [107]. An association between high PAI-1 and atherosclerosis has already been shown [108].

Adipokines potential use in obesity treatment

The potential application of leptin for the treatment of obesity and related disorders of lipid and glucose metabolism is wide and has been considered since the early discovery of this adipokine. Almost immediately, drugs were developed — recombinant human leptin, its analogues, which have been tested on animals and in small number of studies in humans. Studies showed the effectiveness of therapy in a small group of patients with obesity (genetically deficient in leptin synthesis, lipodystrophy), however, the efficiency was low in patients with leptin resistance that is found in up to 95% obese people [109]. Recently Metleptin, an analog of human leptin, has been approved for the treatment of lipodystrophy in Japan. The FDA approved the drug for the treatment of DM and/or hypertriglyceridemia in patients with the rare forms of dystrophy. Later, to overcome leptin resistance, a combination of Metleptin and Pramlintide (analogue of the hormone amylin) have been developed, but human trials were stopped due to side effects [110].

The studies are ongoing, however, it is clear now, since the first drug development, that even when the mechanisms are well known, and efficacy was proven in animal models, its efficacy and safety in humans is not guaranteed.

The synthetic low-molecular weight adiponectin receptor agonists are being developed, e. g. AdipoRon, which improves insulin sensitivity and DM in mice [111].

Visfatin studies in humans have not yet been performed. Visfatin plays an important role in the synthesis of nikotinamidmononucleotide. In mouse models of obesity and DM, introduction of nikotinamidmononucleotide reduces glucose tolerance and increases hepatic insulin sensitivity.

A vaccine against obesity is a challenge that called many attempts [42]. Some studies suggest

that immunization against ghrelin can reduce appetite and body weight. A mice study demonstrated that administration of monoclonal antibodies inhibits ghrelin-mediated acute orexigenic effect, but this effect is not long-lasting [112]. Administration of antibodies against octanoyl fragment of ghrelin leads to the formation of inactive deacylated ghrelin, which leads to more prolonged suppression of appetite [113]. An anti-ghrelin vaccine could be a useful tool for obesity treatment, the effects of long-term neutralization of ghrelin, including perhaps the development of cachexia, need further investigation.

On the other hand, it should be noted that ghrelin administration to patients with cachexia increases appetite and weight, and, thus, improves the prognosis. Ghrelin therapy also might be implemented in patients with heart failure, including those with end-stage disease: ghrelin can increase left ventricular ejection fraction, possibly due to the development of hypertrophy. Intravenous administration of synthetic human ghrelin 2 mg/kg twice daily for three weeks led to an increase in left ventricular ejection fraction due to the increase in myocardial mass and to the reduction in left ventricular end-systolic volume in 10 patients with chronic heart failure. Moreover, there was an increase in lean body mass and muscle strength in these patients [114]. Interestingly, surgical treatment for obesity — gastric bypass — leads to a reduction of body weight, that is partially due to the reduced levels of circulating ghrelin. Ghrelin level is 77% lower in these patients compared to lean subjects [115]. Moreover, there is no daily variability in ghrelin level in these patients, including post-prandial fluctuations. The mechanisms of ghrelin decrease after gastric bypass is unknown.

Conclusions

Nowadays there is an obesity pandemic Diet, physical activity and lifestyle modification cannot always prevent the development of obesity and associated diseases. To develop optimal prevention, molecular mechanisms, underlying these cardiometabolic disorders, should be well studied.

Increased accumulation of adipose tissue in obesity leads to an imbalanced adipokine synthesis, which may play a crucial pathophysiological role in the development of atherosclerosis, hypertension, disorders of carbohydrate metabolism, including type 2 DM, as well as promote further progression of obesity. Effects of adipokines on these processes have been already studied, but many issues are still unclear.

Currently it is known that not all obese individuals are at increased risk of cardiovascular and metabolic complications, and they are considered as «metabolically healthy» obese individuals. Despite an increased adipose tissue mass, such patients have normal sensitivity to insulin, show a normal lipid profile and normal levels of inflammatory markers, as well as normal BP [116]. Few studies showed that some patients with BMI greater than 40 kg/m^2 have elevated levels of adiponectin, which may indicate a metabolic health [117]. So far it is not clear what factors determine the metabolic health even in obese subjects, and the uniform criteria for the definition of «metabolic health» are lacking [118]. Perhaps further study of adipokines in metabolically healthy patients will clarify the mechanisms underlying the absence of negative impact of obesity.

Conflict of interest

Authors declare no conflict of interest.

References

1. Alberti KGMM, Eckel RH, Grundy SM, Grundy SM, Zimmet PZ, Cleeman JI et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity. Circulation. 2009;120(16):1640–1645.

2. Alberti KGMM, Zimmet P. The metabolic syndrome — a new worldwide definition. Lancet. 2005;366(9491):1059–1062.

3. Halberg N, Wernstedt-Asterholm I, Scherer PE. The adipocyte as an endocrine cell. Endocrinol Metab Clin North America. 2008;37(3):753–768.

4. Hsieh CJ, Wang PW, Chen TY. The relationship between regional abdominal fat distribution and both insulin resistance and subclinical chronic inflammation in non-diabetic adults. Diabetol Metab Syndr. 2014;6(1):49.

5. Saleem U, Khaleghi M, Morgenthaler NG, Bergmann A, Struck J, Mosley TH Jr et al. Plasma carboxy-terminal provasopressin (copeptin): a novel marker of insulin resistance and metabolic syndrome. J Clin Endocrinol Metab. 2009;94 (7):2558–2564.

6. Tsimikas S, Willeit J, Knoflach M, Mayr M, Egger G, Notdurfter M et al. Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: results from the Bruneck study. Eur Heart J. 2009;30(1):107–115.

7. Jacobs M, Van Greevenbroek MMJ, Van Der Kallen CJH. et al. Low-grade inflammation can partly explain the association between the metabolic syndrome and either coronary artery disease or severity of peripheral arterial disease: the CODAM study. Eur J Clin Invest. 2009;39(6):437–444.

8. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E et al. Adipocyte death defines macrophage localization

and function in adipose tissue of obese mice and humans. J Lipid Res. 2005;46(11):2347–2355.

9. Lau DCW, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. Am J Physiol Heart Circulat Physiol. 2005;288 (5):2031–2041.

10. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr. 2004;92 (3):347–355.

11. Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res. 2004;94(4):27–31.

12. Hirose H. Serum high-molecular-weight adiponectin as a marker for the evaluation and care of subjects with metabolic syndrome and related disorders. J Atheroscl Thromb. 2010;17 (12):1201–1211.

13. Belyaeva OD, Bazhenova EA, Berezina AV et al. Adiponectin levels, lipid and carbohydrate metabolism in patients with abdominal obesity. Arterial Hypertension = Arterialnaya Gipertenziya. 2009;15(3):309–313 [In Russian].

14. Wynne K, Stanley S, McGowan B. Appetite control. J Endocrinol. 2005;184(2):291–318.

15. Uotani S, Bjorbaek C, Tornoe J, Flier JS. Functional properties of leptin receptor isoforms: internalization and degradation of leptin and ligand-induced receptor downregulation. Diabetes. 1999;48(2):279–286.

16. Gao S, Kinzig KP, Aja S, Scott KA, Keung W, Kelly S et al. Leptin activates hypothalamic acetyl-Co Acarboxylase to inhibit food intake. Proc Natl Acad Sci USA. 2007;104 (44):17358–17363.

17. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. Am J Med Sci. 2005;330 (6):280–289.

18. Chubenko EA, Belyaeva OD, Berkovich OA, Baranova EI. Meaning of leptin in the formation of the metabolic syndrome. Problems of Women's Health = Problemy Zhenskogo Zdorovia. 2010;5(1):45–56 [In Russian].

19. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334(5):292–295.

20. Tschöp M, Wawarta R, Riepl RL, Friedrich S, Bidlingmaier M, Landgraf R et al. Post-prandial decrease of circulating human ghrelin levels. J Endocrinol Invest. 2001;24 (6):19–21.

21. Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating Ghrelin levels are decreased in human obesity. Diabetes. 2001;50(4):707–709.

22. Stepien M, Rosniak-Bak K, Paradowski M, Misztal M, Kujawski K, Banach M et al. Waist circumference, ghrelin and selected adipose tissue-derived adipokines as predictors of insulin resistance in obese patients: preliminary results. Med Sci Monit. 2011;17(11):13–18.

23. Cowley MA, Smith RG, Diano S, Tschöp M, Pronchuk N, Grove KL et al. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron. 2003;37(4):649–661.

24. Oliver P, Picó C, Serra F, Palou A. Resistin expression in different adipose tissue depots during rat development. Mol Cell Biochem. 2003;252(1–2):397–400.

25. Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun. 2003;300(2):472–476.

26. Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV et al. S. Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. Diabetes. 2001;50(10):2199–2202.

27. Lee JH, Chan JL, Yiannakouris N et al. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. J Clin Endocrinol Metab. 2003;88(10):4848–4856.

28. Jain SH, Massaro JM, Hoffmann U, Rosito GA, Vasan RS, Raji A et al. Cross-sectional associations between abdominal and thoracic adipose tissue compartments and adiponectin and resistin in the Framingham Heart Study. Diabetes Care. 2009;32(5):903–908.

29. Berndt J, Kloting N, Kralisch S, Kovacs P, Fasshauer M, Schön MR et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes. 2005;54 (10):2911–2916.

30. Curat CA, Wegner V, Sengen`es C, Miranville A, Tonus C, Busse R et al. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia. 2006;49(4):744–747.

31. Pagano C, Pilon C, Olivieri M, Mason P, Fabris R, Serra R et al. Reduced plasma visfatin/pre-B cell colony-enhancing factor in obesity is not related to insulin resistance in humans. J Clin Endocrinol Metab. 2006;91(8):3165–3170.

32. Haider DG, Holzer G, Schaller G, Weghuber D, Widhalm K, Wagner O et al. The adipokine visfatin is markedly elevated in obese children. J Pediatr Gastroenterol Nutr. 2006;43 (4):548–549.

33. Zahorska-Markiewicz B, Olszanecka-Glinianowicz M, Janowska J et al. Serum concentration of visfatin in obese women. Metabolism. 2007;56(8):1131–1134.

34. Jin H, Jiang B, Tang J, Lu W, Wang W, Zhou L et al. Serum visfatin concentrations in obese adolescents and its correlation with age and high-density lipoprotein cholesterol. Diabetes Res Clin Pract. 2008;79(3):412–418.

35. Michalska M, Iwan-Ziętek I, Gniłka W. PAI-1 and α2-AP in patients with morbid obesity. Adv Clin Exp Med. 2013;22(6):801–807.

36. Natali A, Toschi E, Baldeweg S, Ciociaro D, Favilla S, Saccà L et al. Clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. Diabetes. 2006;55(4):1133–1140.

37. Ma LJ, Mao SL, Taylor KL, Kanjanabuch T, Guan Y, Zhang Y et al. Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. Diabetes. 2004;53(2):336–346.

38. Schaefer K, Fujisawa K, Konstantinides S, Loskutoff DJ. Disruption of the plasminogen activator inhibitor 1 gene reduces the adiposity and improves the metabolic profile of genetically obese and diabetic ob/ob mice. FASEB J. 2001;15 (10):1840–1842.

39. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365(9468):1415–1428.

40. Ianniello F, Quagliozzi L, Caruso A, Paradisi G. Low adiponectin in overweight/obese women: association with diabetes during pregnancy. Eur Rev Med Pharmacol Sci. 2013;17(23):3197–3205.

41. Mojiminiyi OA, Abdella NA. Associations of resistin with inflammation and insulin resistance in patients with type 2 diabetes mellitus. Scand J Clin Lab Invest. 2007;67 (2):215–225.

42. Monteiro MP. Anti-ghrelin vaccine for obesity: a feasible alternative to dieting? Expert Rev Vaccines. 2011;10 (10):1363–1365.

43. Gauna C, Meyler FM, Janssen JA, Delhanty PJ, Abribat T, van Koetsveld P et al. Administration of acylated ghrelin reduces insulin sensitivity, whereas the combination of acylated plus unacylated ghrelin strongly improves insulin sensitivity. J Clin Endocrinol Metab. 2004;89(10):5035–5042.

44. Broglio F, Prodam F, Riganti F, Gottero C, Destefanis S, Granata R et al. The continuous infusion of acylated ghrelin enhances growth hormone secretion and worsens glucose metabolism in humans. J Endocrinol Invest. 2008;31(9):788–794.

45. Steppan CM, Bailey ST, Bhat S. The hormone resistin links obesity to diabetes. Nature. 2001;409(6818):307–312.

46. Walcher D, Hess K, Berger R, Aleksic M, Heinz P, Bach H et al. Resistin: a newly identified chemokine for humanCD4-positivelymphocytes. Cardiovasc Res. 2010;85 (1):167–174.

47. Morash BA, Willkinson D, Ur E, Wilkinson M. Resistin expression and regulation in mouse pituitary. FEBS Lett. 2002;526(1–3):26–30.

48. Qatanani M, Szwergold NR, Greaves DR, Ahima RS, Lazar MA. Macrophage-derived human resistin exacerbates adipose tissue inflammation and insulin resistance in mice. J Clin Invest. 2009;119(3):531–539.

49. Chen BH, Song Y, Ding EL, Roberts CK, Manson JE, Rifai N et al. Circulating levels of resistin and risk of type 2 diabetes in men and women: results from two prospective cohorts. Diabetes Care. 2009;32(2):329–334.

50. Schwartz DR, Lazar MA. Human resistin: found in translation from mouse to man. Trends Endocrinol. Metab. 2011;22(7):259–265.

51. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K et al. Visfatin: a protein secreted by visceral fat that Mimics the effects of insulin. Science. 2005;307(5708):426–430.

52. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K et al. Retraction. Science. 2007;318 (5850):565.

53. Brown JE, Onyango DJ, Ramanjaneya M, Conner AC, Patel ST, Dunmore SJ et al. Visfatin regulates insulin secretion, insulin receptor signalling and mRNA expression of diabetes-related genes in mouse pancreatic β-cells. J Mol Endocrinol. 2010;44(3):171–178.

54. Cheng Q, Dong W, Qian L, Wu J, Peng Y. Visfatin inhibits apoptosis of pancreatic β-cell line, MIN6, via the mitogen-activated protein kinase/phosphoinositide 3-kinase pathway. J Mol Endocrinol. 2011;47(1):13–21.

55. Festa A, D'Agostino RJr, Mykkänen L, Tracy RP, Zaccaro DJ, Hales CN et al. Relative contribution of insulin and its precursors to fibrinogen and PAI-1 in a large population with different states of glucose tolerance. Arterioscler Thromb Vasc Biol. 1999;19(3):562–568.

56. Festa A, Williams K, Tracy RP, Wagenknecht LE, Haffner SM. Progression of plasminogen activator inhibitor-1 and fibrinogen levels in relation to incident type 2 diabetes. Circulation. 2006;113(14):1753–1759.

57. Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment: a position paper of The Obesity Society and the American Society of Hypertension. J Clin Hypertens (Greenwich). 2013;15(1):14–33.

58. Kazumi T, Kawaguchi A, Sakai K, Hirano T, Yoshino G. Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. Diabetes Care. 2002;25(6):971–976.

59. Allison MA, Ix JH, Morgan C, McClelland RL, Rifkin D, Shimbo D et al. Higher leptin is associated with hypertension: the Multi-Ethnic Study of Atherosclerosis. J Hum Hypertens. 2013;27(10):617–622.

60. Vadacca M. Leptin, adiponectin and vascular stiffness parameters in women with systemic lupus erythematosus. Intern Emerg Med. 2013;8(8):705–712.

61. Carlyle M, Jones OB, Kuo JJ, Hall JE. Chronic cardiovascular and renal actions of leptin: role of adrenergic activity. Hypertension. 2002;39(2):496–501.

62. Eikelis N, Schlaich M, Aggarwal A, Kaye D, Esler M. Interactions between leptin and the human sympathetic nervous system. Hypertension. 2003;41(5):1072–1079.

63. Shirasaka T, Takasaki M, Kannan H. Cardiovascular effects of leptin and orexins. Regulatory Integrative Comparative Physiol. Am J Physiol. 2003;284(3):639–651.

64. Singhal A, Farooqi IS, Cole TJ, O'Rahilly S, Fewtrell M, Kattenhorn M et al. Influence of leptin on arterial distensibility: a novel link between obesity and cardiovascular disease? Circulation. 2002;106(15):1919–1924.

65. Matsumura K, Tsuchihashi T, Fujii K, Abe I, Iida M. Central ghrelin modulates sympathetic activity in conscious rabbits. Hypertension. 2002;40(5):694–699.

66. Iglesias MJ, Pineiro R, Blanco M, Gallego R, Diéguez C, Gualillo O et al. Growth hormone releasing peptide (ghrelin) is synthesized and secreted by cardiomyocytes. Cardiovasc Res. 2004;62(3):481–488.

67. Rodrıguez A, Gomez-Ambrosi J, Catalan V, Becerril S, Sáinz N, Gil MJ et al. Association of plasma acylated ghrelin with blood pressure and left ventricular mass in patients with metabolic syndrome. J Hypertens. 2010;28(3):560–567.

68. Ukkola O, Paakko T, Kesaniemi YA. Ghrelin and its promoter variant associated with cardiac hypertrophy. J Hum Hypertens. 2012;26(7):452–457.

69. Vallejo S, Romacho T, Angulo J, Villalobos LA, Cercas E, Leivas A et al. Visfatin impairs endothelium-dependent relaxation in rat and human mesenteric microvessels through nicotinamide phosphoribosyltransferase activity. PLoS One. 2011;6(11): e27299.

70. Zhang L, Curhan GC, Forman JP. Plasma resistin levels associate with risk for hypertension among nondiabetic women. J Am Soc Nephrol. 2010;21(7):1185–1191.

71. Smits MM, Woudstra P, Utzschneider KM, Tong J, Gerchman F, Faulenbach M et al. Adipocytokines as features of the metabolic syndrome determined using confirmatory factor analysis. Ann Epidemiol. 2013;23(7):415–421.

72. Karasek D, Vaverkova H, Halenka M, Jackuliakova D, Frysak Z, Orsag J et al. Prehypertension in dyslipidemic individuals; relationship to metabolic parameters and intima-media thickness. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013;157(1):41–49.

73. Sakamoto M, Suzuki H, Hayashi T, Iuchi H, Isaka T, Sakamoto N et al. Effects of candesartan in hypertensive patients with type 2 diabetes mellitus on inflammatory parameters

and their relationship to pulse pressure. Cardiovasc Diabetol. 2012;11:118.

74. Kim KN, Kim KM, Kim BT, Joo NS, Cho DY, Lee DJ. Relationship of plasminogen activator inhibitor 1 gene 4G/5G polymorphisms to hypertension in Korean women. Chin Med J (Engl). 2012;125 7):1249–1253.

75. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscl Thromb Vasc Biol. 2004;24(1):29–33.

76. Xydakis AM, Case CC, Jones PH, Hoogeveen RC, Liu MY, Smith EO et al. Adiponectin, inflammation, and the expression of the metabolic syndrome in obese individuals: the impact of rapid weight lose through caloric restriction. J Clin Endocrinol Metab. 2004;89(6):2697–2703.

77. Lee HS, Lee M, Joung H. Adiponectin represents an independent risk factor for hypertension in middle aged Korean women. Asia Pacific J Clin Nutrition. 2007;16(1):10–15.

78. Pala L, Monami M, Ciani S, Dicembrini I, Pasqua A, Pezzatini A et al. Adipokines as possible new predictors of cardiovascular diseases: a case control study. J Nutr Metab. 2012;2012:253428. doi: 10.1155/2012/253428

79. Wu ZJ, Cheng YJ, Gu WJ, Aung LH. Adiponectin is associated with increased mortality in patients with already established cardiovascular disease: A systematic review and meta-analysis. Metab Clin Experiment. 2014;63(9):1157–1166.

80. Cooke JP, Oka RK. Does leptin cause vascular disease? Circulation. 2002;106(15):1904–1905.

81. Park HY, Kwon HM, Lim HJ, Hong BK, Lee JY, Park BE et al. Potential role of leptin in angiogenesis: leptin induces endothelial cell proliferation and expression of matrix metalloproteinases in vivo and in vitro. Exp Mol Med. 2001;33(2):95–102.

82. Artwohl M, Roden M, Holzenbein T, Freudenthaler A, Waldhäusl W, Baumgartner-Parzer SM. Modulation by leptin of proliferation and apoptosis in vascular endothelial cells. Int J Obes Relat Metab Disord. 2002;26(4):577–580.

83. O'Rourke L, Gronning LM, Yeaman SJ, Shepherd PR. Glucose-dependent regulation of cholesterol ester metabolism in macrophages by insulin and leptin. J Biol Chem. 2002;277 (45):42557–42562.

84. Sierra-Honigmann MR, Nath AK, Murakami C, García-Cardeña G, Papapetropoulos A, Sessa WC et al. Biological action of leptin as an angiogenic factor. Science. 1998;281 (5383):1683–1386.

85. Van Dielen FMH, Van't Veer C, Schols AM, Soeters PB, Buurman WA, Greve JW. Increased leptin concentrations correlate with increased concentrations of inflammatory markers in morbidly obese individuals. Intern J Obes. 2001;25 (12):1759–1766.

86. Konstantinides S, Schafer K, Koschnick S, Loskutoff DJ. Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity. J Clin Invest. 2001;108(10):1533–1540.

87. Tesauro M, Schinzari F, Iantorno M, Rizza S, Melina D, Lauro D et al. Ghrelin improves endothelial function in patients with metabolic syndrome. Circulation. 2005;112(19):2986–2992.

88. Li WG, Gavrila D, Liu X, Wang L, Gunnlaugsson S, Stoll LL et al. Ghrelin inhibits proinflammatory responses and nuclear factor-kappaB activation in human endothelial cells. Circulation. 2004;109(18):2221–2226.

89. Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Imai Y et al. Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. Biochem Biophys Res Commun. 2004;314(2):415–419.

90. Lee TS, Lin CY, Tsai JY, Wu YL, Su KH, Lu KY et al. Resistin increases lipid accumulation by affecting class A scavenger receptor, CD36 and ATP-binding cassette transporter-A1 in macrophages. Life Sci. 2009;84(3–4):97–104.

91. Piestrzeniewicz K, Łuczak K, Komorowski J, Maciejewski M, Jankiewicz Wika J, Goch JH. Resistin increases with obesity and atherosclerotic risk factors in patients with myocardial infarction. Metabolism. 2008;57(4):488–493.

92. Choi HY, Kim S, Yang SJ, Yoo HJ, Seo JA, Kim SG et al. Association of adiponectin, resistin, and vascular inflammation: analysis with 18F-fluorodeoxyglucose positron emission tomography. Arterioscler Thromb Vasc Biol. 2011;31(4):944–949.

93. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation. 2005;111(7):932–939.

94. Ohmori R, Momiyama Y, Kato R, Taniguchi H, Ogura M, Ayaori M et al. Associations between serum resistin levels and insulin resistance, inflammation, and coronary artery disease. J Am Coll Cardiol. 2005;46(2):379–380.

95. Wang H, Chen DY, Cao J, He ZY, Zhu BP, Long M. High serum resistin level may be an indicator of the severity of coronary disease in acute coronary syndrome. Chin Med Sci J. 2009;24(3):161–166.

96. On YK, Park HK, Hyon MS, Jeon ES. Serum resistin as a biological marker for coronary artery disease and restenosis in type 2 diabetic patients. Circ J. 2007;71(6):868–873.

97. Krecki R, Krzeminska-Pakula M, Peruga JZ, Szcześniak P, Lipiec P, Wierzbowska-Drabik K et al. Elevated resistin opposed to adiponectin or angiogenin plasma levels as a strong, independent predictive factor for the occurrence of major adverse cardiac and cerebrovascular events in patients with stable multivessel coronary artery disease over 1-year follow-up. Med Sci Monit. 2011;17(1):26–32.

98. Momiyama Y, Ohmori R, Uto-Kondo H, Tanaka N, Kato R, Taniguchi H et al. Serum resistin levels and cardiovascular events in patients undergoing percutaneous coronary intervention. J Atheroscler Thromb. 2011;18(2):108–114.

99. Cabrera de León A, Almeida González D, González Hernández A, Juan Alemán Sánchez J, Brito Díaz B, Domínguez Coello S et al. The association of resistin with coronary disease in the general population. J Atheroscler Thromb. 2014;21 (3):273–281.

100. Vanhoutte PM. Endothelial dysfunction: the first step toward coronary arteriosclerosis. Circul J. 2009;73 (4):595–601.

101. Kong QX, Xia M, Liang RQ, Li L, Cu X, Sun Z et al. Increased serum visfatin as a risk factor for atherosclerosis in patients with ischaemic cerebrovascular disease. Singapore Med J. 2014;55(7):383–387.

102. Dahl TB, Yndestad A, Skjelland M, Øie E, Dahl A, Michelsen A et al. Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. Circulation. 2007;115(8):972–980.

103. Kim SR, Bae SK, Choi KS, Park SY, Jun HO, Lee JY et al. Visfatin promotes angiogenesis by activation of extracellular signal-regulated kinase ½. Biochem Biophys Res Communications. 2007;357(1):150–156.

104. Xiao J, Xiao ZJ, Liu ZG, Gong HY, Yuan Q, Wang S et al. Involvement of dimethylarginine dimethylaminohydrolase-2

in visfatin-enhanced angiogenic function of endothelial cells. Diabetes Metab Res Rev. 2009;25(3):242–249.

105. Moulton KS. Angiogenesis in atherosclerosis: gathering evidence beyond speculation. Curr Opin Lipidol. 2006;17(5):548–555.

106. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H et al. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol. 2007;178(3):1748–1758.

107. Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. N Engl J Med. 2000;342 (24):1792–1801.

108. Schneiderman J, Sawdey MS, Keeton MR, Bordin GM, Bernstein EF, Dilley RB et al. Increased type 1 plasminogen activator inhibitor gene expression in atherosclerotic human arteries. Proc Natl Acad Sci USA. 1992;89(15):6998–7002.

109. DePaoli AM. 20 years of leptin: leptin in common obesity and associated disorders of metabolism. J Endocrinol. 2014;223(1):71–81.

110. Amylin Pharmaceuticals, Inc.Takeda Pharmaceutical Company Limited Amylin and Takeda Discontinue Development of Pramlintide/Metreleptin Combination Treatment for Obesity Following Commercial Reassessment of the Program. Newsroom. July-September 2011.

111. Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K et al. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature. 2013;503(7477):493–499.

112. Lu SC, Xu J, Chinookoswong N, Liu S, Steavenson S, Gegg C et al. An acyl-ghrelin-specific neutralizing antibody inhibits the acute ghrelin-mediated orexigenic effects in mice. Mol Pharmacol. 2009;75(4):901–907.

113. Mayorov AV, Amara N, Chang JY, Moss JA, Hixon MS, Ruiz DI et al. Catalytic antibody degradation of ghrelin increases whole-body metabolic rate and reduces refeeding in fasting mice. Proc Natl Acad Sci USA. 2008;105(45):17487–17492.

114. Nagaya N, Moriya J, Yasumura Y, Uematsu M, Ono F, Shimizu W et al. Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation. 2004;110(24):3674–3679.

115. Cummings DE, Weigle DS, Frayo RS et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002;346(21):1623–1630.

116. Alfadda AA. Circulating adipokines in healthy versus unhealthy overweight and obese subjects. Int J Endocrinol. 2014;2014:170434. doi: 10.1155/2014/170434

117. Aguilar-Salinas C, García E, Robles L, Riaño D, Ruiz-Gomez DG, García-Ulloa AC et al. High adiponectin concentrations are associated with the metabolically healthy obese phenotype. J Clin Endocrinol Metab. 2008;93 (10):4075–4079.

118. Karelis AD. Metabolically healthy but obese individuals. Lancet. 2008;372(9646):1281–1283.