



Adiponectin, Resistin and Leptin: Possible Markers of Metabolic Syndrome John Zhang¹, Pronyuk KHO^{1,2,}, Kuliesh OV^{1,2} and Shi Chenghe³

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Abstract

The metabolic syndrome is a major and escalating public-health and clinical challenge worldwide. Most studies show that the MS is associated with an approximate doubling of cardiovascular disease risk and a 5-fold increased risk for incident type 2 diabetes mellitus. Adipose tissue is actively involved in metabolic processes and secretes adiposederived factors named adipokines. Adipokines have been linked to the pathogenesis of MS and its comorbidities. This study was established to estimate the use of adipocytokines as early markers of metabolic disorders. 70 participants were enrolled into the study, divided into two groups depending on presence of MS. It has been demonstrated that plasma adiponectin concentrations correlate negatively with HOMA-IR, the relationship of blood lipid disorders and level of adiponectin were shown in MS patients. Resistin levels rise in parallel with increase in BMI in overweight and obese MS patients; significant correlation between elevated resistin levels and HOMA-IR index were shown. Leptin levels were significantly higher in patients with metabolic syndrome.

Keywords: Metabolic syndrome; Adipokines; Adiponectin; Resistin; Leptin; Obesity; Insulin resistance

Introduction

During last decades in the medical literature actively is discussed the combination of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality and is known as Metabolic Syndrome (MS). The MS includes the clustering of abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure and is associated with other comorbidities including the prothrombotic state, proinflammatory state, nonalcoholic fatty liver disease, and reproductive disorders. At the present time researches of MS become especially actual due to pandemic character of its spreading [1].

The metabolic syndrome is a major and escalating public-health and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits [2-4]. The prevalence of the MS is increasing to epidemic proportions not only in the remainder of the urbanized world but also in developing nations. The prevalence of MS varied from 8% to 43% in men and from 7% to 56% in women around the world [2]. In general, it is estimates that one-quarter of the world's adult population has the MS. Most studies show that the MS is associated with an approximate doubling of cardiovascular disease risk and a 5-fold increased risk for incident type 2 diabetes mellitus [2,3].

MS is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are factors which constitute the syndrome.

Idea about adipose tissue as an inert organ whose function is only to accumulate and preserve energy substrate, has been left long in the past. Recent studies have shown that adipose tissue is actively involved in metabolic processes and produces a huge amount of hormonally active substances, which have various biological effects and can affect the activity of metabolic processes in tissues, both directly and indirectly through the neuroendocrine system, interacting with the hormones of hypophysis, catecholamines, insulin. An important role in the pathogenesis of metabolic syndrome play hormones produced in white adipose tissue. According to current knowledge in adipose tissue activated macrophages produce cytokines – TNF-alfa and

Interleukin-6 (IL-6), C-reactive protein, intercellular adhesion factor 1, platelet-endothelial adhesion factors, monocyte chemoattractant 1 and coagulation factors (plasminogen activator inhibitor 1, PAI-1) are secreted. Besides, adipose tissue secretes polypeptide hormones - leptin, adiponectin, resistin and ferments that control biosynthesis and activation of steroid hormones. These substances have a multidirectional impact on the organism and in case of disturbances in interaction, contribute development of obesity associated diseases such as hypertension, atherosclerosis, Type II diabetes mellitus (T2DM). In general, factors secreted by adipose tissue have common name adipokines [5,6]. It is known that adipokines play an important role in a control of liver, pancreas function, glucose and lipids metabolism, restoring of tissue sensitivity to insulin and disorders in their balance can initiate MS [7-9]. A list of adipokines, that are secreted by adipose tissue and are considered as possible markers of MS includes: leptin, adiponectin and resistin.

Leptin is a multifunctional hormone of adipose tissue secreted by adipocytes. Leptin is usually called the saturation hormone, since it takes part in controlling of energy exchange and body weight [10]. It decreases food intake and increases energy consumption by acting on specific hypothalamic nuclei, inducing anorexigenic factors and suppressing orexigenic neuropeptides [11,12]. Obese people have higher level of circulated leptin, which occurs on a background of leptin resistance [13]. Leptin resistance and hyperleptinemia take important role in the development of Insulin Resistance (IR). Activation of lipolysis in visceral fat caused by hyperlipidemia and activation of the sympathetic nervous system, leads to accumulation of free fatty acids that inhibit the release of insulin from β -cells of the pancreas and increase glucose tolerance. In fat cells, stimulation of β -receptors results in a decrease

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Received November 30, 2015; Accepted December 16, 2015; Published December 30, 2015

Citation: Zhang J, Pronyuk KHO, Kuliesh OV, Chenghe S (2015) Adiponectin, Resistin and Leptin: Possible Markers of Metabolic Syndrome. Endocrinol Metab Syndr 4: 212. doi:10.4172/2161-1017.1000212

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in glucose transport into cells. Thus, development of leptin resistance and a decrease of circulating levels of leptin receptor in obesity leads to the fact those even high levels of leptin in the blood cannot realize their insulin-sensitizing effects [14-16]. However, at present time the relation between leptin and insulin levels are studied, but data remains controversial [17,18]. The most of authors supposes that the most important role in regulating the secretion of leptin belongs to insulin, by increasing insulin levels above physiological marked increase in the concentration of leptin [10,19]. At the same time, according to several other authors, variations in the levels of leptin and insulin throughout the day negatively correlated [20,21]. Currently, research continues to study the clinical aspects of leptin action, that in the future will allow to study of the role of leptin in the formation of metabolic disorders in details.

One of key adipokines is adiponectin. Adiponectin is a peptic hormone, that the same as leptin is secreted in adipocytes of adipose tissue, plays an important role in the regulation of carbohydrate and fat metabolism in insulin-sensitive tissues, performing the function of endogenous insulin-sensitizer [22]. It increases fatty acid oxidation and glucose uptake in the muscle and reduces the synthesis of glucose in the liver. Its secretion is inhibited by pro-inflammatory cytokines, suggesting that inflammation might be an important factor contributing to hypo-adiponectinemia in insulin-resistant and obese states. The deficiency of adiponectin leads to insulin-resistance's progression, obesity, T2DM and atherosclerosis [23-25].

It is also known that adiponectin reduces in plasma concentrations of low density lipoproteins, apolipoprotein B, enhances their metabolism, due to the influence of adiponectin on lipid metabolism in skeletal muscle [26]. Furthermore, a number of clinical studies have shown that adiponectin has a significant vasodilator impact, and against the background of hypertension can have an antihypertensive effect, and hypoadiponectinemia can lead to arterial hypertension [26]. There have been a number of studies proved the role of adiponectin in the development and progression of chronic heart failure in patients with obesity [27]. It is thought that in the context of obesity, along with IR, resistance to adiponectin developed, which can complicate the treatment of obesity and the ineffectiveness of therapeutic interventions [28].

Resistin is a relatively new and poorly studied adipokine. It is secreted primary by preadipocytes and less by mature preadipocytes of abdominal localization and macrophages [29,30]. Some authors indicated that increased serum resistin levels are associated with increased obesity, visceral fat, insulin resistance, and T2DM, while other groups failed to observe such correlations [31,32]. In experimental researches it is shown that injection of recombinant resistin leads to disorder of glucose tolerance, and immunoneutralization by antibodies of endogenic resistin improves the insulin sensitivity. It was also found that resistin neutralize the inhibitory effect of insulin on glucose production by the liver and reduces glucose uptake by skeleton muscles independently of glucose transporters (GLUT-4) [33]. Determining the level of resistin may serve to identify predisposition to T2DM and obesity, resistin antagonists can be used to treat these conditions. At the same time, the question of the role of resistin in formation of insulin resistance, associated with obesity, is a difficult task, due to the presence of a number of conflicting data. The problem of the participation of resistin in the regulation of insulin sensitivity in humans is, at present, poorly understood.

Objective

This study was established to estimate the use of adipocytokines, namely, leptin, adiponectin and resistin as early markers of metabolic

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disorders, by finding correlative relationships with the major components of MS.

Materials and Methods

Participants in the study were recruited from healthy volunteers and patients attending Shenzhen Any Check Clinic and clinic of O.O. Bogomolets National Medical University. 70 participants were enrolled into the study, of these, 36 women and 34 men aged 18 to 60 years (mean age was 30.9 ± 1.2 years). Participants were divided into two groups depending on presence of MS. Basic group consisted of 50 patients with the presence of MS, control group consisted of 20 health volunteers. Diagnostic of MS was carried out according to the criteria of International Diabetes Federation/IDF. For the diagnostic of overweight/obesity Body Mass Index (BMI) was used which calculated as weight/height² (kg/m²). Basic group included 19 persons with a BMI: $25-30 \text{ kg/m}^2$ that is regarded as overweight (pre-obese), 16 persons with BMI: $30-35 \text{ kg/m}^2$, that corresponds to the first degree of obesity and 15 persons with BMI: $35-40 \text{ kg/m}^2$, that corresponds to the second degree of obesity.

Assessment of carbohydrate metabolism was based on fasting glucose and insulin levels. Blood glucose was measured by enzymatic method on biochemical analyzer «Spectrum II» Abbott, USA, insulin level was measured via immunofluorescent method with Delfia diagnostic kit, Finland. The presence of hyperglycemia was fixed at the level of blood glucose above 6.1 mmol/l.Insulin resistance was assessed using the homeostasis model assessment ratio (HOMA-R) formula derived from fasting insulin and glucose levels. IR was diagnosed at the index HOMA level > 2.7.

Assessment of lipid profile performed on Total Cholesterol levels (TC), Triglycerides (TG), High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL), which was determined by enzymatic method on biochemical analyzer «Spectrum II» Abbott, USA. Evaluation of lipoprotein levels was conducted according to criteria, which were proposed in the Third report on the treatment of dyslipidemia in adults (Adult treatment Panel – ATP-III) and National Cholesterol Education Program.

Plasma levels of resistin, adiponectin and leptin were determined by ELISA using a standard set BioVendor (Germany).

Statistical analysis was performed using Statistisa software package for Windows 5.5 (StatSoft Inc., 2000). Quantitative indicators are presented as medians, quality indicators - in the form of the absolute number of observations and the proportion (in%) of number of examinees in the corresponding group or the total number examined. To examine the relationship between quantitative indices used method of Spearman rank correlation. Comparing quantitative performed using Kruskal-Wallis test (for three or more groups) or Mann-Whitney (two groups). Level of statistical significance was chosen to be 0.05.

Results

When comparing the basic (group 1, n=50) and control (group 2, n=20) groups, with an acceptable level of significance (p<0.05), differences were revealed in anthropometric data (BMI), blood lipid parameters (triglycerides, HDL cholesterol,), glycaemia and insulin levels, HOMA index. The anthropometric and metabolic characteristics of patients and controls are shown in Table 1.

Plasma adiponectin levels were decreased significantly in patients with MS compared with control subjects (Table 1). Correlation analysis showed inverse correlation between HOMA-IR and adiponectin levels in patients with metabolic syndrome (r=0,360; p=0,003). The negative correlation between plasma adiponectin and BMI was significant after adjusting for age and gender. Was established the presence of the inverse correlation between TC, TG and adiponectin levels in patients with MS: TC and adiponectin (r=-0,24, p<0,05), TG and adiponectin (r=-0,28, p<0,05) and positive association with HDL (r=0,43; p<0,01), which was confirmed by other studies that have shown the relationship of blood lipid disorders in patients with the metabolic syndrome and T2DM and level of adiponectin.

Serum leptin is closely associated with obesity and diabetes, has a functional role in the pathogenesis of severe illness and clearly correlates with markers of glucose and lipids metabolism. Leptin levels were significantly higher in patients with metabolic syndrome (Table 1). Leptin levels were correlated significantly with BMI (r=0,732, p<0,001) and HOMA-IR in patients with MS. Also, a significant correlation was observed between leptin and resistin. HDL-C was associated with high level of plasma leptin.

Higher levels of resistin were observed in MS cases when compared to controls (12.43±4.73 vs 6.99±1.98). Resistin positively correlated with BMI (r=0,74; p<0,001). A comparative analysis of resistin levels in patients with varying degrees of obesity showed a tendency to increase its levels with increasing of BMI. Plasma resistin levels showed positively and significant associated with insulin (r=0.74; p<0,001) and HOMA-IR (r=0.40; p<0,001). Study of resistin and blood lipids levels showed positive association with total cholesterol and negative association with HDL levels (r=0.33; p<0.05 vs r=0,26; p<0.05).

Conclusions

It is apparent that the pathogenesis of MS is complex and multifactorial in which several adipocytokines have been implicated. In was shown that levels of resistin and leptin were significantly higher and plasma adiponectin levels were significantly lower in MS patients compared to healthy controls.

Study confirmed previous findings that obesity is associated with low plasma adiponectin concentrations; significant negative correlation between BMI and plasma adiponectin levels was shown in patients with MS. It has been demonstrated that plasma adiponectin concentrations correlate negatively with HOMA-IR, the relationship of blood lipid disorders and level of adiponectin were shown in patients with metabolic syndrome. Resistin levels rise in parallel with increase in BMI in overweight and obese MS patients; significant correlation between elevated resistin levels and HOMA-IR index, correlation with lipids profiles was shown. It was shown that leptin levels are directly associated with insulin resistance and BMI in patients with metabolic

Data	l (basic group) (n=50)	II (control group) (n=20)
Age. years	31.0 ± 7.0	29.7 ± 4.3
BMI, kg/m ²	31.9 ± 3.4**	21.9 ± 2.5
Insulin µU/mL	10.3 ± 1.0 [⊷]	3.8 ± 0.6
HOMA-IP	2.8 ± 0.3 [⊷]	1.2 ± 0.2
TC, mmol/l	5.5 ± 1.2	4.8 ± 1.3
TG, mmol/l	1.9 (1.2; 2.8)**	0.9 (0.6; 1.2)
HDL-C, mmol/l	1.2 ± 0.3*	1.5 ± 0.4
LDL-C, mmol/l	3.6 ± 1.0	2.9 ± 1.2
Resistin, ng/mL	12.43 ± 4.73*	6.99 ± 1.98
Adiponectin, mg/l	$8.6 \pm 0.8^{\circ}$	13.5 ± 1.7
Leptin, mg/l	26.7 ± 3.6"	5.8 ± 0.7
[*] p<0.05; ^{**} p<0.001.		

 Table 1: Anthropometric and metabolic characteristics of patients and controls.

syndrome. Adiponectin, leptin and resistin may be suitable markers for predicting metabolic syndrome.

Acknowledgements

This work was supported by the grant from Shenzhen 2013 Overseas High Level Talents "Peacock" project (20130409 173324816); "Guangdong Provincal Science and Technology Plan" Project (508191 654026); "Technology development and creative design of Nanshan District, Shenzhen" project (504164 797019).

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