Research Article

Serum uric acid and leptin levels in metabolic syndrome

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ABSTRACT

This study investigates the impact of serum uric acid (UA) and serum leptin on the risk factors associated with metabolic syndrome. In addition, this study explores the relationship between serum uric acid and serum leptin in metabolic syndrome. 191 metabolic syndrome patients (111 men and 80 women) were recruited from several medical centers in Damascus, metabolic syndrome was defined using an international diabetes federation (IDF) criteria, and 74 healthy subjects (32 men and 42 women) as a control group. Obesity factors (body mass index, waist circumference, waist to hip ratio), insulin resistance (HOMA-IR and fasting insulin), Uric acid, leptin and 6MS-related parameters (triglycerides, cholesterol, LDL-C, HDL-C, fasting Glucose and diastolic and systolic blood pressure) were measured. Serum uric acid levels were significantly higher in metabolic syndrome group in both sexes compared with control group, and positively correlated with triglycerides, body mass index, HOMA-IR, insulin, waist circumference, waist to hip ratio, systolic blood pressure and leptin in both sexes. This study has showed that statically there was not a significant correlation between UA and cholesterol, LDL-C, HDL-C, Glucose and diastolic blood pressure in both sexes. Serum leptin levels were significantly higher in metabolic syndrome group in both sexes compared with control group, and positively correlated with body mass index, HOMA-IR, insulin, waist circumference, and waist to hip ratio in both sexes. Statistically, there was not a significant correlation between serum leptin and triglycerides, cholesterol, LDL-C, HDL-C, Glucose and blood pressure in both sexes. There was a statically positive correlation was found between UA and Leptin in both sexes.

Keywords: Metabolic Syndrome, Uric acid, Leptin.

INTRODUCTION

Metabolic syndrome is a clustering of multiple risk factors for cardiovascular disease such as central obesity, glucose intolerance or type 2 diabetes mellitus, hypertriglyceridemia, low high-density lipoprotein (HDL-C), and hypertension[1]. It has been postulated that insulin resistance is a key underlying pathophysiologic abnormality in this condition[2]. Serum uric acid is an important factor in cardiovascular events[3]. Hyperuricemia reflects insulin resistance[4-5]. Some large epidemiologic studies have suggested that serum uric acid levels should be included in the definition of metabolic syndrome[2-6]. Increased serum uric acid levels are often accompanied by obesity, dyslipidemia, and hypertension[7].

Leptin, a cytokine product of the ob gene, is secreted into the blood from adipocytes[8] once released into the circulation; leptin lowers body weight by decreasing appetite and altering metabolic processes[9]. Leptin influences appetite, energy expenditure, and neuroendocrine axes via a high affinity receptor expressed mainly in hypothalamus, but also in other tissues[10]. Leptin deficiency or defective leptin signaling, due to mutation in the genes encoding leptin (ob) and the leptin receptor (obR), cause severe obesity in rodents. In human obesity, however, ob mRNA abundance, leptin secretion from adipose tissue, and circulating leptin concentrations are increased, and are positively correlated with the degree of obesity[11]. This suggests that resistance to leptin, rather than leptin deficiency, is common in obese patients[12]. The secretion of leptin seems to be modulated by several factors including sex, age, insulin, glucocorticoids, catecholamines, cytokines (TNF, interleukin1) and smoking[13]. Basal leptin levels are markedly elevated in obese subjects, implying an association between high leptin and the characteristic obesity complications known as the metabolic syndrome[14].

In this study we compared serum uric acid UA and serum leptin as the risk factors associated with metabolic syndrome between people with and without metabolic syndrome. In addition, this study explores the relationship between serum uric acid and serum leptin in metabolic syndrome.

MATERIALS AND METHODS

Subjects

191 metabolic syndrome patients (111 men and 80 women) were recruited from several medical centers in Damascus; metabolic syndrome was defined using an international diabetes federation (IDF) criteria as following:

Waist circumference (as a prerequisite): male ≥ 94 cm, female ≥ 80 cm

Plus any two of the following:

• Triglycerides ≥ 150 mg / dL or specific treatment for this abnormality

• HDL: Men < 40 mg / dL, women < 50 mg / dL or specific treatment for this abnormality

• High blood pressure ≥ 130/85 mmgh or medication for hypertension

• Fasting plasma glucose ≥ 100 mg / dL or previously diagnosed type 2 diabetes samples were collected during 8 months from 4 April 2011 to 24 January 2012. Mean (X) and Standard Division (SD) for ages in males (X± SD: 49± 2.12) years and in females (X ±SD: 46±6.36) years. Each participant was interviewed by a physician, who obtained a detailed medical history and elicited dietary habits and lifestyle characteristics (including smoking status, exercise status, and alcohol consumption). All patients don't /do not use any drugs which affect the studied parameters.

Measurements

Systolic (SBP) and diastolic (DBP) blood pressure were measured twice in the right arm using a mercury sphygmomanometer with the patient in the supine position after resting for at least 5 minutes. Individual SBP and DBP were calculated as the mean of the two measurements.

Biochemistry

For all kinds of measurements, fasting venous blood was collected and the sera used immediately after separation. Serum uric acid, glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C) using a Hitachi 747 autoanalyser (Hitachi, Tokyo) with dedicated reagents. Measurement of Serum insulin was measured by Electro Chemiluminiscence Assay (ECLIA) and leptin levels was measured by Leptin (Sandwich) ELISA using DRG kit.

HOMA-IR was defined using the following formula: (Fasting Insulin µU/mL x Fasting Glucose mg/dl) / 405

Anthropometry

Height and weight were measured using standard techniques while the subject was wearing light clothes and bare-footed. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. The body mass index was calculated as weight in kilograms divided by the square of height in meters. The waist circumference was measured midway between the lower rib and the iliac crest, and the hip circumference at the level of the great trochanters, the waist to hip ratio (WHR) was calculated as the ratio between the waist and the hip circumferences.

Statistical analyses

All statistical analyses were performed using the SPSS-PC program (version 7.5, Chicago, IL, USA). Adopted t-Test for the Significance of the Difference between the Means.

Also, was used Pearson correlation coefficient to study the correlation between the studied parameters and $P < 0.05$ was considered statistically significant.

Table 1: Characteristics and Profiles of the study population

Variable	Patients	Controls	p-value
Uric acid-males	6.99 mg / dl	5.32 mg / dl	P<0.001
Uric acid-females	6.12 mg / dl	3.98 mg / dl	P<0.001
Leptin -males	18.88 ng / mL	5.45 ng / mL	p=0.012
Leptin-females	28.26 ng / mL	9.34 ng / mL	p=0.004
triglycerides	282.52 mg / dl	144.33 mg / dl	P<0.001
Total cholesterol	217 mg / dl	180.13 mg / dl	P<0.001
LDL-C	138.68 mg / dl	106.34 mg / dl	P=0.013
HDL-C	38.52 mg / dl	55.79 mg / dl	P=0.008
Glucose	138 mg / dl	88.39 mg / dl	P<0.001
BMI-males	35.89 kg / m 2	26.10 kg/m2	P=0.006
BMI-females	33.12 kg / m 2	24.82 kg/m2	P=0.0016
insulin	29.65 µIU/mL	10.55 µIU/mL	P<0.001
HOMA-IR	9.83	2.28	P<0.001
Waist circumference - males	113.08 cm	93.67 cm	P=0.032
Waist circumference - females	105.11 cm	80.81 cm	P=0.041
Systolic blood pressure	13.84mmhg	12.3mmhg	P=0.031
Diastolic blood pressure	8.88 mmhg	7.87 mmhg	P=0.038
WHR- males	1.05	0.91	P=0.042
WHR- females	0.92	0.82	P=0.007

RESULTS

Compared to the values of the variables studied between the patient group and the control group was seen in table 1.

When examining the correlation of uric acid with metabolic syndrome and after the partition of study groups to males and females we found the findings are:

In males:

There was a significant positive correlation between serum uric acid levels and:

Triglycerides (R = 0.46, P <0.001), BMI (R = 0.21, P <0.020), HOMA-IR (R = 0.34, P <0.001), insulin (R = 0.49, P = 0.007), waist circumference (R=0.47, P<0.001), WHR(R=0.28, P<0.002), Systolic blood pressure (R=0.13, P<0.001).

In females:

There was a positive correlation between serum uric acid levels and:

Triglycerides (R=0.54, P<0.001), BMI (R=0.31, P<0.001), HOMA-IR (R = 0.32, P <0.001), insulin (R=0.30, P= 0.007), waist circumference (R=0.26, P= 0.002), WHR(R=0.32, P<0.039), Systolic blood pressure (R=0.13, P= 0.004).

Statistically, there was not a significant correlation between UA and total cholesterol, LDL-C, HDL-C, Glucose and diastolic blood pressure in both sexes.

When studying the role of leptin as a risk factor, and as an additional component of metabolic syndrome; plays a vital role in insulin resistance. The levels of serum leptin were clearly found to be higher and statistically significant in patients with metabolic syndrome, males and females, compared with the control group of the same sex.

In males:

Serum leptin levels was positively correlated with body mass index (R=0.28, P=0.002), HOMA-IR (R=0.32, P<0.001), insulin (R=0.3, P= 0.020), waist circumference(R=0.25, P= 0.008), and waist to hip ratio (R= 0.606, P<0.001).

In females:

Serum leptin levels was positively correlated with body mass index (R=0.53, P<0.001), HOMA-IR (R=0.63, P<0.020), insulin (R=0.28, P= 0.011), waist circumference(R=0.29, P= 0.008), and waist to hip ratio (R= 0.22, P=0.012).

Statistically, there was not a significant correlation between leptin and triglycerides, total cholesterol, LDL-C, HDL-C, Glucose, systolic and diastolic blood pressure in both sexes.

There was significant positive correlation between serum uric acid and serum leptin in males (R=0.2, P=0.031) and in females (R=0.23, P=0.006).

DISCUSSION

Serum Uric acid levels in metabolic syndrome

This study has shown the significant relationships between serum UA and 5 components of the metabolic syndrome.

Direct association of SUA levels with MetS and IR

Several studies revealed that IR is inversely related to 24-hour urinary UA clearance[15]. Therefore, one mechanism linking hyperinsulinemia (a consequence of IR) with hyperuricemia is a decreased renal excretion of UA. In fact, insulin can enhance renal tubular sodium reabsorption in humans[16]. Furthermore, renal excretion of UA is reduced in situations with increased renal tubular reabsorption of sodium[17]. This finding could be explained by the fact that proximal tubular reabsorption of UA occurs by an active transport mechanism closely linked to, or identical with, the tubular reabsorption of sodium[17]. Moreover, insulin receptors have been found in different tubular segments[18]. Whatever the site of the tubular effects of insulin, possible mechanisms include direct stimulation of tubular ion exchange or acceleration of cellular metabolism[19]. Therefore, insulin can modify the handling of UA by the kidney, so that leading to hyperuricemia. In the same context, it has been recently shown that patients with MetS exhibited significantly lower serum phosphate and magnesium levels compared with healthy individuals [20].

In addition, there are other mechanisms connecting increased SUA levels and hyperinsulinemia. Indeed, increased purine biosynthesis and turnover, with its attendant increase in SUA concentrations caused by increased activity of the hexose monophosphate shunt, may be linked to IR and/or hyperinsulinemia[21]. Specifically, impairment of the glycolytic pathway can increase flux of glucose- 6-phosphate through the hexose monophosphate shunt, resulting in accumulation of ribose-5-phosphate and other intermediates, which are major substrates for UA production[22]. Furthermore, glucose-6-phosphatase deficiency has been reported to be associated with increased SUA levels through multiple mechanisms [22].

On the other hand, there is evidence that UA may not only be a consequence of IR, but it may actually promote or worsen IR. Specifically, a recent study[23] has shown that UA plays an important role in the pathogenesis of MetS, possibly due to its ability to inhibit endothelial function. In detail, UA has been shown to inhibit nitric oxide (NO) bioavailability[24]. That is because insulin requires NO to stimulate glucose uptake, the investigators hypothesized that hyperuricemia may have a key role in the pathogenesis of IR[23]. Furthermore, experiments from the same group confirmed the above statement. Firstly, they have demonstrated that fructose intake can induce features of MetS (hyperinsulinemia, hypertriglyceridemia) and also hyperuricemia. Moreover, they have administrated allopurinol (a xanthine oxidase inhibitor)

and noticed that this drug could prevent fructose induced hyperinsulinemia and hypertriglyceridemia[23].

Metabolic syndrome is associated with increased oxidative stress[25] and CVD risk[26]. That is because UA is considered to be an effective antioxidant[27], the elevated SUA levels encountered in individuals with MetS may reflect a compensatory mechanism counteracting the increased oxidative stress associated with the MetS.

Other factors may also contribute to the association of elevated SUA levels with MetS. Serum uric acid concentration may depend on food and alcohol intake [28]. Undoubtedly, alcohol abuse may increase urate generation[29] and decrease urate excretion[30] resulting in hyperuricemia. Furthermore, a diet rich in purines (eg, overconsumption of meat and seafood), complex carbohydrates, and saturated fat may lead to both MetS and hyperuricemia[31]. Commonly used drugs, such as diuretics, may also lead to elevated SUA levels[31]. In addition, postmenopausal women have higher incidence of hypertension, diabetes, obesity, and MetS as well as hyperuricemia. A possible explanation is that estrogen is uricosuric[32].

Indirect association of SUA levels with MetS and IR Hypertension, commonly encountered in MetS, could mediate an indirect relationship between MetS and SUA levels. Indeed, hypertension could lead to hyperuricemia by several mechanisms[33]. Hypertension leads to vascular disease and increased renal vascular resistance[33], both resulting in decreased renal blood flow, which in turn stimulates urate reabsorption. Moreover, microvascular disease leads to local ischemia and release of lactate, which compete with urate transporter in the proximal tubule, thus blocking urate excretion[33]. In addition, ischemia induces the degradation of adenosine to adenine and xanthine, whereas increased generation of xanthine oxidase may be observed [22]. The increased generation of the substrate (xanthine) and the enzyme (xanthine oxidase) can lead to increased UA production[34]. Furthermore, high SUA levels have been associated with an increased generation of free radicals[35] and oxidative stress, which may abolish endothelium dependent vasodilatation, thus leading to hypertension[36]. However, as already stated, other studies have suggested that UA is an effective antioxidant [27]and elevated SUA levels encountered in individuals with MetS may reflect a compensatory mechanism to the increased oxidative stress associated with the MetS. One possible mechanism could be that xanthine oxidase, the enzyme responsible for UA production, is one of the main producers of reactive oxygen species in the endothelium. All things considered, the exact role of UA in oxidation (ie, antioxidant vs prooxidant) is largely unknown and remains to be elucidated. Uric acid may not only be the result, but also a mediator of hypertension[37]. Endothelial dysfunction and impaired NO production due to increased SUA levels, as well as the possible proinflammatory and prooxidative capacity of UA may explain the pathogenic role of UA in hypertension. In addition, large clinical trials demonstrated that UA predicts renal dysfunction, which is associated with the development of hypertension[38].

The absence of a relationship between serum uric acid levels and diastolic pressure in this study could be explained because the values of diastolic blood pressure were close to other while differences in systolic blood pressure values were clearer and broader.

Hypertriglyceridemia is one of the main abnormalities in MetS. The association between UA and IR may be secondary to the association between UA levels and hypertriglyceridemia. Many studies have underlined the independent association of TRG and SUA levels[39]. In this context, increased TRG levels may be associated with decreased UA renal excretion [39].

Several studies have revealed a genetic association between hypertriglyceridemia and hyperuricemia. Apolipoprotein (Apo) E polymorphism may affect SUA levels; the ApoE2 allele was independently associated with increased SUA levels in healthy individuals in one study[40]. On the other hand, an uncommon allelic variant of the ApoC-III gene (S2 allele) as well as the ApoE4 allele[41] have been found more frequently in individuals with elevated TRG and SUA levels. In addition, a recent study has shown that patients with MetS who do not have the E3/3 genotype have a greater risk of hyperuricemia and postprandial hypertriglyceridemia after a fat overload[42]. The above findings suggested that the association between high UA and TRG levels may be partially genetic.

Dyslipidemia per se represents a significant aggravating factor for renal dysfunction[43]. Atherogenic dyslipidemia (increased TRGs, decreased HDL-C levels, and, consequently, increased small-dense low-density lipoprotein cholesterol particle concentration) is a common characteristic of the MetS. High serum cholesterol binds to glomerular mesangial cells, and this may lead to renal function decline. A reduction in glomerular filtration rate is another mechanism that increases SUA[44]. The above mechanism could also partially explain the association between dyslipidemia and hyperuricemia.

Serum leptin levels in metabolic syndrome

This study has found that statistically, the levels of serum leptin were significantly higher in metabolic syndrome patients compared with the control group in both sexes. serum leptin Levels were higher in males compared with females groups and this could explain the existence of a direct effect of estrogen in increasing the production of leptin, and the proportion of body fat in females than males who have the same BMI, and men generally have higher metabolic activity This leads to increased hormonal response and lower resistance to leptin[45].

The significant positive correlation between serum leptin levels and WHR indicates the role of leptin in regulating central obesity, also considered WHR important biomarker between central obesity and many related

diseases[46]. The negative correlation between leptin and age could be interpreted that there are other most important variables that can regulate the concentration of leptin in the blood, including physical activity and types of food and insulin and other hormones.

The link between Leptin and metabolic syndrome

The visceral adipose tissue (VAT) obesity in metabolic syndrome could explain the high levels of serum leptin in metabolic syndrome patient. Serum leptin levels in obese people are significantly higher than in lean ones. Many studies demonstrated that leptin levels Increase with BMI in males and females[48]. It is now established that leptin is an anorexigenic peptide which fails to break Food intake in case of resistance to it's by the hypothalamic centers[48].

The positive correlation between total body fat mass and serum leptin is probably explained primarily by the increased release of leptin from large cells compared with small fat cells. On average, leptin released per gram of adipose tissue is two times greater in obese than in lean subjects. Because fat cell size is usually enlarged 2–4 times in the obese, when expressed per fat cell, leptin secretion is up to 7 times higher in obese than in lean subjects. In addition, an increased number of fat cells, particularly in extreme obesity, undoubtedly contribute to increases in serum leptin[49]. The relationship that existed in our study between uric acid and leptin.

Obesity is one of the most important components of the metabolic syndrome, many studies have shown that obesity and increased waist circumference associated with hyperuricemia, Bedir *et al.* showed that leptin might be responsible for excessive uric acid associated with obesity[50].

Possible mechanisms that could explain the relationship between leptin and uric acid: Firstly, leptin directly affects renal function, whose causes directly reduce the excretion of uric acid, low calorie diets, weight loss lead to rapid decrease of serum leptin levels, and increase the excretion of uric acid. Secondly, serum uric acid can modify leptin levels by increasing the expression for an obesity gene[51], or can reduce the leptin clearance[52].

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