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Original Research Paper

Diabetology

THE RELATIONSHIP BETWEEN URIC ACID AND INSULIN, HOMA-IR AND HOMA-β

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ABSTRACT

Introduction: According to previous cross-sectional and longitudinal analysis studies done by our team, serum uric acid (UA) was higher in subjects with metabolic syndrome (MetS). We hypothesis that this correlation was through low grade inflammation and cause insulin resistance. Therefore, in the current study, we are trying to investigate the relationship between serum uric acid level, serum insulin level, beta-cell function, and insulin resistance in both genders.

Methods: We randomly selected 1,021 subjects at first. Subjects with history of hypertension, duabetes, cardiovascular event and were taking medications known to affect MetS components were all excluded. Finally, a total of 864 subjects were eligible for further analysis. Homeostasis Model Assessment-Insulin Resistance index (HOMA-IR) and Homeostasis Model Assessment β-cell function index (HOMA-β) were also calculated.

Results: UA and HOMA-IR were independtly having higher risks of developing MetS. Therefore, we want to know which MetS factors were correlated with UA to contribute the risk of having MetS. Multiple regression analysis was done and we found waist circumference, fasting plasma glucose and tryglyceride in male and age, waist circumference, and high density lipoprotein in female were independently correlated with UA.

Conclusion: UA is a independent risk factor fir developing MetS. This mechanism was not through insulin resistance which HOMA-IR was wash-out in multiple regression analysis. Further studies are needed to exlopring the underlying mechanisms.

KEYWORDS : Uric acid, metabolic syndrome, HOMA

INTRODUCTION

Metabolic syndrome (MetS) is a group of symptoms such as central obesity, insulin resistance, high blood pressure, and hyperlipidemia [1]. According to the World Health Organization, the prevalence of childhood obesity worldwide has more than tripled during the past four decades [2].

Uric acid (UA) is the final product of purine metabolism and is secreted by the kidneys. The increase in UA levels may be due to a decrease function in the kidneys. Hyperinsulinemia has been postulated to decrease uric acid clearance by the kidneys [3] Nitric oxide (NO) is an important endothelial-derived relaxation factor involved in oxidative stress and resistance. UA reduces NO, the known mechanism that triggers insulin resistance by impairs endothelial function and lead to the lack of synthetic NO [4]. UA has also been shown to be involved in cardiovascular disease in adults with or without impaired glucose tolerance [5].

In the recent years, serum UA, as a predictive biomarker and risk factor of MetS, has received much attention from researchers, like other classical risk factors (eg, glycaemia, TG and HDL-C) [6-10]. Many studies have demonstrated that elevated UA level is linked with hypertension, diabetes, obesity, insulin resistance and MetS [6-13].

According to previous cross-sectional and longitudinal analysis studies done by our team, UA was higher in subjects with MetS [14-16]. We hypothesis that this correlation was through low grade inflammation and cause insulin resistance. Therefore, in the current study, we are trying to investigate the relationship between serum UA level, serum insulin level, beta-cell function, and insulin resistance in both genders.

MATERIALS AND METHODS

Study Population

We enrolled subjects from cardinal Tien hospital from 2015~2016. Data from the participants were collected anonymously, and informed consents were obtained before health checkup. The study protocol was approved by the Institutional Review Board and the data were provided for research purposes only. We randomly selected 1,021 subjects at first. Subjects with history of hypertension, DM, cardiovascular event and were taking medications known to affect MetS components were all excluded. Finally, a total of 864 subjects were eligible for further analysis.

Anthropometric measurements and general data

A standard protocol of the checkup was followed in the hospital. The senior nursing staff in the clinic used a questionnaire to obtain the subject's medical history, including any current medications. Then, complete physical examinations were performed. Waist circumference (WC) was measured horizontally at the level of the natural waist, which was identified as the level at the hollow molding of the trunk when the trunk was laterally concave. Body mass index (BMI) was calculated as the subject's body weight (kg) divided by the square of the subject's height (m). Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the nursing staff using a standard mercury sphygmomanometer fitted on the right arm of each subject when seated. Laboratory measurements after the subject fasted for 10 hours, blood samples were drawn from the antecubital vein for biochemical analysis. Plasma was separated from blood within 1 hour and stored at -30℃ and analyzed for fasting plasma glucose (FPG) and lipid profiles. The FPG was detected using a glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Springs Instruments, Yellow Springs, OH). Insulin was measured by using automated analyzer. Total cholesterol and triglycerides (TG) were measured using the dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentration were analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation. Hemoglobin A1c (HbA1c) was measured with an Abbott Cell Dyn 3000 hematology analyzer (Abbott Laboratories, Abbott Park, IL, USA). Homeostasis

Model Assessment-Insulin Resistance index (HOMA-IR) and Homeostasis Model Assessment β-cell function index (HOMA-β) were also calculated.

Definition of metabolic syndrome

We used the latest harmonized criteria of MetS in 2009 with some modification [17]. The WC ≧ 90 and 80 cm in Taiwanese men and women respectively [2].Other four criteria were the same: SBP ≧ 130 mmHg or DBP ≧ 85 mmHg, TG ≧ 150 mg/dL, FPG ≧ 100 mg/dL, HDL ≦ 40 and 50 mg/dL in men and women or taking related medications. Subjects had to have at least three criteria to be diagnosed as MetS.

STATISTICAL ANALYSIS

The data in this study are presented as mean ± standard deviation. All data were tested for normal distribution with Kolmogorov–Smirnov test and homogeneity of variances with Levene's test. The t –test was used to evaluate the differences between the two groups. Logistic regression for odds ratio was used. Correlations between factors were evaluated by Pearson correlation. In order to evaluate the independent factors, multiple logistic regression was applied. A p-value (two-sided) < 0.05 was considered to be significant. All statistical analyses were performed by using SPSS 23.0 software (SPSS Inc., Chicago, IL).

RESULTS

Demographic data of study subjects with and without metabolic syndrome were shown in the table 1.

Table 1 Demographic data of study subjects with and without metabolic syndrome

	MetS (-)			MetS (+)			P value
Male							
n	392			180			
Age (year)	54.2	±	0.5	54.8	±	0.8	0.507
Waist circumference (cm)	87.4	±	0.4	95.9	±	0.6	< 0.001
Body mass index (Kg/m2)	24.5	±	0.1	27.5	±	0.3	< 0.001
Systolic blood pressure (mmHg)	117.3	±	0.6	127.5	±	1.3	< 0.001
Diastolic blood pressure (mmHg)	71.3	±	0.5	77.3	±	0.9	< 0.001
Fasting plasma glucose (mg/dl)	94.7	±	0.8	113.1	±	2.6	< 0.001
HbA1c (%)	5.67	±	0.03	6.24	±	0.09	< 0.001
Insulin (μU/ml)	7.25	±	0.34	10.45	±	0.61	< 0.001
HOMA-IR	1.73	±	0.09	2.91	±	0.18	< 0.001
HOMA-β (%)	88.71	±	3.44	93.88	±	5.76	0.420
Total cholesterol (mg/dl)	200.7	±	1.7	199.3	±	2.7	0.644
High density lipoprotein (mg/dl)	44.9	±	0.4	38.0	±	0.5	< 0.001
Triglyceride (mg/dl)	116.5	±	3.1	187.9	±	6.8	< 0.001
Low density lipoprotein (mg/dl)	122.8	±	1.6	121.6	±	2.6	0.680
Uric acid (mg/dl)	6.59	±	0.07	7.07	±	0.10	< 0.001
Female							
n	216	76					
Age (year)	52.9	±	0.7	59.9	±	1.1	< 0.001
Waist circumference (cm)	82.6	±	0.5	90.6	±	1.0	< 0.001
Body mass index (Kg/m2)	22.7	±	0.2	25.5	±	0.4	< 0.001
Systolic blood pressure (mmHg)	110.3	±	0.9	125.1	±	2.1	< 0.001
Diastolic blood pressure (mmHg)	65.9	±	0.6	73.3	±	1.3	< 0.001
Fasting plasma glucose (mg/dl)	88.4	±	0.5	110.0	±	3.0	< 0.001
HbA1c (%)	5.48	±	0.02	6.10	±	0.10	< 0.001
Insulin (μU/ml)	4.91	±	0.21	9.49	±	0.77	< 0.001
HOMA-IR	1.09	±	0.05	2.62	±	0.25	< 0.001
HOMA-β (%)	68.54	±	4.80	87.47	±	8.46	0.054
Total cholesterol (mg/dl)	208.4	±	2.4	207.4	±	4.4	0.835
High density lipoprotein (mg/dl)	55.7	±	0.9	44.0	±	1.0	< 0.001
Triglyceride (mg/dl)	88.3	±	2.7	164.0	±	8.7	< 0.001
Low density lipoprotein (mg/dl)	117.3	±	2.2	123.3	±	4.0	0.186
Uric acid (mg/dl)	5.05	±	0.08	5.84	±	0.15	< 0.001

HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β= homeostatic model assessment of β-cell function

Generally, factors with MetS were higher or worse when compared with subjects without MetS. Especially UA had the same result. However, HOMA-β, total cholesterol and LDL were non-significant in both genders. Odds ratio of having MetS was shown in table 2.

Table 2 Odds ratio of having metabolic syndrome by metabolic syndrome components, insulin parameters and uric acid

	Male			Female		
	Odds Ratio (95% Confidence Interval)			Odds Ratio (95% Confidence Interval)		
Systolic blood pressure	1.049*	(1.035	-1.063)	1.062*	(1.041	-1.083)
Diastolic blood pressure	1.057*	(1.037	-1.076)	1.075*	(1.045	-1.106)
Waist circumference	1.158*	(1.124	-1.193)	1.126*	(1.084	-1.170)
Fasting plasma glucose	1.041*	(1.029	-1.054)	1.149*	(1.105	-1.195)
High density lipoprotein	0.871*	(0.843	-0.899)	0.890*	(0.859	-0.922)
Triglyceride	1.013*	(1.010	-1.016)	1.026*	(1.019	-1.034)
HOMA-IR	1.384*	(1.233	-1.554)	3.282*	(2.319	-4.645)
HOMA-β	1.001	(0.999	-1.003)	1.005*	(1.000	-1.009)
Insulin	1.066*	(1.035	-1.098)	1.263*	(1.170	-1.364)
Uric acid	1.287*	(1.129	-1.466)	1.634*	(1.316	-2.030)

* p < 0.01

HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β = homeostatic model assessment of β -cell function

All parameters were significantly with higher risk having MetS in both genders including UA, insulin, HOMA-IR (Table 3).

Table 3 Multivariant analysis of having metabolic syndrome by insulin resistance and uric acid

	Male			Female		
	Odds Ratio (95% Confidence Interval)			Odds Ratio (95% Confidence Interval)		
Uric acid	1.266*	(1.106	-1.449)	1.451*	(1.131	-1.862)
HOMA-IR	1.369*	(1.220	-1.536)	3.084*	(2.170	-4.381)

* p < 0.01

HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β = homeostatic model assessment of β -cell function

However, HOMA-β in male fail to showed significance. When we further explore which factors were independtly act as a risk factors of having MetS, both UA and HOMA-IR were significantly having higher risks. Therefore, we want to know which MetS factors were correlated with UA to contribute the risk of having MetS. Simple correlation of individual Mets component, insulin parameters and UA was done (Table 4).

Table 4 Simple correlation between parameters and uric acid

	Male		Female	
	β	p value	β	p value
Age	- 0.033	0.431	0.357	< 0.001
Systolic blood pressure	0.014	0.739	0.177	0.002
Diastolic blood pressure	0.016	0.711	0.156	0.007
Body mass index	0.175	< 0.001	0.351	< 0.001
Waist circumference	0.199	< 0.001	0.406	< 0.001
Fasting plasma glucose	- 0.083	0.047	0.179	0.002
Hemoglobin A1c	- 0.084	0.045	0.285	< 0.001
Total cholesterol	0.108	0.009	0.110	0.059
High density lipoprotein	- 0.172	< 0.001	- 0.249	< 0.001
Low density lipoprotein	0.078	0.061	0.189	0.001
Triglyceride	0.265	< 0.001	0.297	< 0.001
HOMA-IR	0.072	0.086	0.254	< 0.001
HOMA-β	0.073	0.080	- 0.043	0.457
Insulin	0.091	0.030	0.251	< 0.001

HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β = homeostatic model assessment of β-cell function

We found BMI, WC, FPG, HbA1c, Total cholesterol, HDL, TG, and insulin were correlated with UA in male. Age, SBP, DBP, BMI, WC, FPG, HbA1c, HDL, LDL, TG, HOMA-IR and insulin were correlated with UA in female. Similarly, multiple regression analysis was done to see which factors were independently correlated with UA (Table 5).

Table 5 Multivariant regression analysis between parameters and uric acid

	r	p value
Male		
Waist circumference	0.137	0.002
Fasting plasma glucose	- 0.139	0.001
High density lipoprotein	- 0.073	0.096
Triglyceride	0.222	< 0.001
HOMA-IR	0.043	0.330
Female		
Age	0.252	< 0.001
Systolic blood pressure	- 0.046	0.610
Diastolic blood pressure	0.062	0.477
Waist circumference	0.240	< 0.001
Fasting plasma glucose	- 0.041	0.505
High density lipoprotein	- 0.126	0.033
Triglyceride	0.108	0.078
HOMA-IR	0.057	0.390

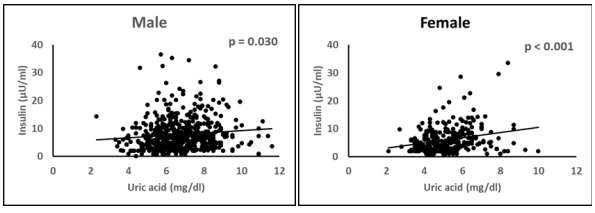

Figure 1 Scatter plot of uric acid and insulin level

We found WC, FPG and TG in male and age, WC, and HDL in female were independently correlated with UA. HOMA-IR was washed out in multiple regression which means UA is a truly risk factor for MetS. This mechanism was not through insulin resistance which HOMA-IR was not correlated with UA. The figure 1 showed scatter plot of UA and insulin. Significant correlation was identified in both genders.

DISCUSSION

In our study, via simple correlation analysis we found that UA level was significantly positive correlated to components of Mets, such as WC, SBP, DBP, TG and FPG level in both gender, which was consistent with previous study [18]. We also found that UA level was correlated to plasma insulin level in both gender with statistically significance. Besides, in female group, we found that higher UA level was correlated to higher HOMA-IR value, which is an indicator of insulin resistance. The same trend was also noted in male group while the P value was 0.08. Furthermore, we found that UA level has no significant correlation to HOMA-B in both genders, in other words, UA had no impact on pancreatic beta cell function.

Previous studies reported that there was a significant relationship between UA and the incidence of MetS [19, 20]. Some studies also noted that high serum UA could lead to insulin resistance [21, 22], and as we know, insulin resistance are believed to be at the core of most cases of MetS [23]. Present study is to determine whether UA level and insulin resistance could be two independent factors of Mets or just two sides to one coin, which plays an key role in design or modified the prediction model of Mets.

This can be a two-way model for the relationship between insulin resistance and hyperuricemia. In other words, insulin resistance can increase the level of UA and worsen insulin resistance. Previous studies have shown that insulin resistance is associated with plasma xanthine oxidoreductase (XOR) activity. In humans, XOR is known to be expressed in the liver and intestines but not in visceral fat. XOR is a rate-limiting enzyme for in vivo uric acid production that catalyzes oxidation not only from hypoxanthine to xanthine but also from xanthine to uric acid in the purine metabolism pathway [24].

The relationship between insulin resistance and hyperuricemia is independent of visceral adiposity and adiponectin level, suggesting that the development of insulin resistance resulting from increased visceral adiposity and/or reduced serum adiponectin contributes to increased UA production by stimulating XOR activity [25]. Animal studies have shown that increasing insulin can directly enhanced XOR activity [26]. Moreover, hyperglycemia can also directly stimulate XOR activity in the liver and increase UA levels in diabetic patients [27]. Furthermore, insulin resistance is considered to increase ribose-5-phosphate production by impairing the glycolysis pathway through reduced glyceraldehyde-3-phosphate dehydrogenase activity and increase adenosine triphosphate degradation to adenosine monophosphate, suggesting that insulin resistance indirectly activates XOR activity in the liver via enhanced purine degradation [28, 29]. Insulin-mediated renal reabsorption of UA has been shown to be reduced UA excretion by the consequences of insulin resistance.

On the other hand, high UA can worsen insulin resistance. In previous studies, soluble UA may increase tissue levels of NADPH oxidase and production of reactive oxygen species (ROS) in mature and oxidatively stressed adipose tissue. Increased ROS is a risk factor for insulin resistance [31]. Other animal models and human cell studies have shown that acute hyperuricemia may reduce insulin sensitivity in mice model [32]. The possible mechanism could be increased UA activates ROS production, increased oxidative stress, and phosphorylation of IRS-1. This activity causes Akt phosphorylation and causes acute insulin resistance in the liver after hyperuricemia [32].

In our simple correlation analysis of the relationship between UA and MetS components, we found significant relation between higher UA level and HOMA-IR in female group, but non-significant in male. There was cross-sectional observation study of 102 outpatient subjects done by Adnan et al. in 2019 pointed out that UA level had no significant difference in insulin resistance and non-insulin resistance group, however, this study did not regard gender as a variation in analysis [20].

In our multivariant regression analysis between parameters of Mets and uric acid, we found that in male group, only serum TG had significant relation with serum UA. In female group, only WC had significant relation with serum UA. In both male and female groups, not only serum insulin level but HOMA-IR, (which is a more relative index of insulin resistance) and HOMA-B (which is a indicator of beta cell function) had no significant relation to serum UA. In the other word, despite the complex two-way relationship between serum uric acid and insulin resistance, these are two independent variables of MetS, which could be very important in building a prediction model of MetS.

In conclusion, UA is a independent risk factor fir developing MetS. This mechanism was not through insulin resistance which HOMA-IR was wash-out in multiple regression analysis. Further studies are needed to exlopring the underlying mechanisms.

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