Association of Elevated Serum Uric Acid with the Components of Metabolic Syndrome and Oxidative Stress in Abdominal Obesity Subjects

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Abstract Abdominal obesity (AO) and metabolic syndrome (MetS) are associated with the cardiovascular disease and type 2 diabetes. Serum uric acid (SUA) is often elevated in subjects with the AO. We aimed to investigate the association of elevated SUA with the components of MetS, oxidative stress and TG/HDL-C ratio in AO subjects. This cross-sectional study used data from a Health Survey for Prevention of Hypertension and Type 2 Diabetes Mellitus in residents of two districts in Phitsanulok province, including 443 subjects. Anthropometric, blood pressure (BP) and biochemical variables were measured. We categorized the participants to two-group as 248 AO subjects (median age = 58, interquartile range 50.0–65.0 years) and 195 non-AO subjects (median age = 53, interquartile range 47.0–62.0 years). Waist circumference was significantly correlated with SystBP, DiastBP, Glu and SUA ($P < 0.05$) and SUA was significantly correlated with Glu, TG, HDL-C and TG/HDL-C ratio ($P < 0.05$). By using multiple logistic regression, we found the association of elevated SUA with abdominal obesity, hyperglycemia, hypertriglyceridemia, reduced

HDL-C, elevated TG/HDL-C ratio, MetS and increased oxidative stress after adjusting for their covariates. Our study demonstrated that circulating UA is a major antioxidant and might help protect against free-radical oxidative damage. However, elevated SUA concentrations associated with oxidative stress, MetS, insulin resistance, and components of MetS. Then, SUA may be a marker of increased oxidative stress, insulin resistance and MetS, implying an increased risk of vascular disease and T2DM.

Keywords Abdominal obesity · Uric acid · Metabolic syndrome · TG/HDL-C ratio · Oxidative stress

Introduction

Abdominal obesity (AO) and the metabolic syndrome (MetS) are frequently associated with the prevalence of cardiovascular disease (CVD) [1]. Serum uric acid (SUA) is often elevated in subjects with the MetS and it increases according to uric acid levels in large epidemiological studies [2, 3]. Many studies have quantitatively estimated the risk assigned uric acid concentrations and the clustering of MetS components in adult and elderly populations [2, 3]. Uric acid is the final product of purine nucleotides metabolism, in mammals uricase present in the liver converts urate into allantoin, substantially reducing uric acid plasma levels. Finally, uric acid is eliminated by the kidney. Further studies showed that most individuals had hyperuricemia, but not gout [4] and reported its association with obesity, hypertension (HT), dyslipidemia, kidney and CVD and more recently with the MetS [5].

Obesity, especially of visceral fat, has been recognized as a major underlying factor of the pathogenesis of several diseases, including metabolic syndrome, insulin resistance,

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type 2 diabetes, HT, dyslipidemia, atherosclerosis and several forms of cancer [6, 7]. In human studies, the extent of fat accumulation has been correlated with various markers of systemic oxidative stress [8]. Studies have shown that oxidative stress is directly and indirectly associated with the pathogenesis of insulin resistance via the inhibition of insulin signals and the dysregulation of adipocytokines/adipokines, respectively [9, 10]. Oxidative stress occurs when reactive oxygen/nitrogen species overwhelm the antioxidant defense system. This is observed as a change in the organism's redox status that favors a disproportionate increase in reactive species or a decrease in the antioxidant defense [10]. If reactive species are not scavenged by antioxidants, they react with other cellular components [11]. The consequences of such detrimental reactions include lipid peroxidation, protein modification, and DNA oxidation [12]. Oxidative stress is purported to be involved in the pathogenesis of obesity-associated insulin resistance. Uric acid is a major antioxidant and might help protect against free-radical oxidative damage [13]. We aimed to investigate the association between elevated SUA levels with the components of MetS, increased oxidative stress and TG/HDL-C ratio in AO subjects.

Materials and Methods

Subjects

This cross-sectional study used the data from Health Survey for Prevention of HT and Type 2 Diabetes Mellitus in residents of two districts in Phitsanulok Province (January 2010–2013). Four hundred and forty three participants (114 men and 329 women) participated in the present study. We excluded the 94 subjects with known end stage renal failure, cancer, infection and any life threatening diseases from the study. We categorized to two-group as 248 AO subjects (median age = 58, interquartile range 50.0–65.0 years), waist circumference (WC) ≥ 90 cm in men and ≥ 80 cm in women and 195 non-abdominal obesity (non-AO) subjects (median age = 53, interquartile range 47.0–62.0 years), WC < 90 cm in men and < 80 cm in women according to the consensus definition of International Diabetes Federation (IDF) [14]. All participants were apparently healthy with no clinical signs of associated pathologies or organ damage and no history of coronary or cerebrovascular atherosclerotic disease. All participants gave written informed consent, and the Ethics Committee of Naresuan University approved the study protocol.

Anthropometric and Blood Pressure Measurement

Anthropometric parameters i.e. height, weight, and BP were measured and body mass index (BMI) was calculated. Waist

circumference was measured at the midpoint between the both of rib cage and the top of lateral border of iliac crest during minimal respiration. Blood pressure was measured as the mean value of at least two measurements of these participants on the same day with a Terumo digital blood pressure monitor (ES-P110). Hypertension was defined as an average BP $\geq 140/90$ mmHg or if the participant was taking antihypertensive medications or had been diagnosed with HT.

Definition of Metabolic Syndrome

Metabolic syndrome was defined according to the consensus definition of IDF [14]. Men with a WC in excess of 90 cm and women with a WC in excess of 80 cm were diagnosed with MetS if they had two or more of the following components: (1) dyslipidemia: triglycerides ≥ 150 mg/dl and/or HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women; (2) high blood pressure: BP $\geq 130/85$ mmHg; (3) impaired glucose tolerance: fasting plasma glucose ≥ 100 mg/dl.

Blood Sample Collection and Biochemical Determination

Venous blood samples were collected without stasis after a 12 h fast and a 30 min rest in a supine position. Blood specimens were processed and assayed on the central laboratory of Faculty of Allied Health Sciences on the same day. Fasting plasma glucose (Glu), Uric acid, total cholesterol (TC), triglycerides (TG), and high density lipoprotein cholesterol (HDL-C) were determined by the enzymatic methods on the Hitachi 912 autoanalyzer (Roche Diagnostic, Switzerland). Low density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's equation, which is valid for TG values less than or equal to 400 mg/dl. We defined subjects as having hyperuricemia if their SUA concentration was > 7.0 mg/dl (in men) or > 6.0 mg/dl (in women) [15].

Triglyceride to High-density Lipoprotein Cholesterol (TG/HDL) Ratio

TG/HDL-C ratio has been identified as a reliable marker of insulin resistance in overweight, obesity and T2DM patients [16, 17]. The cut-off value was 2.50, measuring concentrations in mg/dl. TG/HDL-C ratio has the best specificity and sensitivity [17], taking the method of steady-state plasma glucose as reference.

Apolipoprotein B (ApoB) Assay

An immunoturbidimetric assay was procedurally measured by using a Hitachi 912 auto-analyzer (Roche Diagnostic,

Switzerland). Method is standard IFCC SP3-07 procedure [18]. No high-dose hook effect was observed up to an ApoB concentration of 6.00 g/L (22.7 μ mol/L). The method produced excellent within-run precision at (mean $\pm$ SD) 0.29 ± 0.004 g/L, (%CV = 1.5); 1.12 ± 0.006 g/L (%CV = 2.5); 1.27 ± 0.014 g/L (%CV = 1.1).

Malondialdehyde (MDA) Assay

After thawing the samples, MDA level was determined by using the thiobarbituric acid substances (TBARS) assay, a spectroscopic technique as in our previous report [19]. The method is based on the formation of red (pink) chromophore following the reaction of TBA with MDA and the other breakdown products of peroxidized lipids called MDA. One molecule of MDA reacts with two molecules of TBA to yield a pink pigment with absorption maximum at 532 nm.

Statistical Analysis

Statistical analysis was performed using the SPSS computer program version 13.0 (SPSS, Chicago, IL, USA). All variables are expressed as median and interquartile range (Q1–Q3). The Mann–Whitney *U* test was used to estimate difference between groups. Spearman rank correlation was used to assess the bivariate correlation of SUA with all components of MetS and other biochemical variables. All significant higher variables were identified as risk factors (WC, BP, Glu, SUA, TG, HDL-C, LDL-C, TG/HDL-C and MDA) for CVD and diabetes, and SUA was analyzed by multiple logistic regression to determine their contributions

to the risk of MetS. Tests were two-tailed, and a *P* value < 0.05 was considered significant.

Results

Of these study participants, 248 (%) were AO subjects. We found that SystBP, DiastBP, WC, BMI, Glu, SUA, TC, TG, TG/HDL-C, ApoB and MDA levels were significantly higher and HDL-C level was lower in AO than Non-AO (*P* < 0.05) as shown in Table 1. Bivariate correlations showed that WC was significantly correlated with BMI, SystBP, diastBP, Glu and SUA (*r* = 0.680, *P* < 0.01; *r* = 0.172, *P* = 0.007; *r* = 0.135, *P* < 0.001; *r* = 0.212, *P* = 0.001, *r* = 0.224, *P* < 0.001, respectively), SUA was significantly correlated with Age, SystBP, Glu, TG, ApoB, HDL-C, and TG/HDL-C (*r* = 0.194, *P* = 0.002; *r* = 0.178, *P* = 0.005; *r* = 0.188, *P* = 0.003; *r* = 0.216, *P* = 0.001, *r* = 0.205, *P* = 0.001, *r* = −0.179, *P* = 0.005 and *r* = 0.221, *P* < 0.001, respectively) in AO subjects and the correlation of the other variables were demonstrated in Table 2. Multiple logistic regression was used to calculate the association of elevated SUA with (A-1) Abdominal obesity, (A-2) hyperglycemia, (A-3) hypertriglyceridemia, (A-4) reduced HDL-C, (A-5) elevated TG/HDL-C ratio (A-6) MetS, and (B) Increased oxidative stress after adjusting for their covariates as shown in Table 3. Increased SUA concentrations in AO subjects were significantly associated with AO, elevated Glu, elevated TG, reduced HDL-C, elevated TG/HDL-C ratio, MetS and elevated MDA levels; ORs and 95 % CIs were 3.18 (1.97, 5.15), 2.62 (2.29, 5.36), 3.18 (1.78, 5.69), 2.11 (1.12, 3.96), 2.19 (1.36, 3.51),

Table 1 Comparison of the general characteristics of abdominal obesity and non-abdominal obesity subjects

Variables	AO subjects (<i>n</i> = 248)	Non-AO subjects (<i>n</i> = 195)	<i>P</i> value
Age (years)	58.0 (50.0–65.0)	53.0* (47.0–62.0)**	0.001
SystBP (mmHg)	132.5 (121.25–147.0)	120.0 (109.0–133.0)	<0.001
DiastBP (mmHg)	81.0 (75.0–91.0)	75.0 (67.0–83.0)	<0.001
WC (cm)	89.0 (84.0–95.0)	76.0 (72.0–81.0)	<0.001
BMI (kg/m ²)	26.37 (24.41–29.02)	21.75 (20.14–23.7)	<0.001
Glu (mmol/l)	5.78 (5.39–6.42)	5.17 (4.95–5.50)	<0.001
SUA (mmol/l)	351.05 (293.04–420.67)	297.50 (243.95–357.00)	<0.001
TC (mmol/l)	5.727 (5.056–6.521)	5.160 (4.619–6.063)	<0.001
TG (mmol/l)	1.857 (1.254–2.644)	1.153 (0.836–1.514)	<0.001
HDL-C (mmol/l)	1.338 (1.141–1.647)	1.639 (1.365–1.963)	<0.001
LDL-C (mmol/l)	3.319 (2.719–3.929)	2.954 (2.363–3.589)	<0.001
TG/HDL-C ratio	3.26 (1.957–5.106)	1.505 (1.102–2.444)	<0.001
ApolipoproteinB (g/l)	1.003 (0.833–1.195)	0.811 (0.698–0.974)	<0.001
MDA (μ mol/l)	7.10 (4.20–10.20)	4.40 (3.30–8.25)	<0.001
HT (62, 14 %)	51 (%)	11 (%)	<0.001
DM (65, 14.7 %)	43 (%)	22 (%)	<0.001

* Median; ** interquartile range (Q1–Q3)

Table 2 Bivariate correlation between parameters in abdominal obesity subjects using Spearman rank correlation

Correlation between parameters	Correlation coefficient	
	R	P value
WC		
BMI	0.680	<0.001
SystBP	0.172	0.007
DiastBP	0.135	<0.001
Glu	0.212	0.001
SUA	0.224	<0.001
TC		
Age	0.140	0.028
SystBP	0.167	0.008
DiastBP	0.177	0.005
TG	0.256	<0.001
HDL-C	0.169	0.008
ApoB	0.815	<0.001
Glu		
Age	0.250	<0.001
TC	0.209	0.001
SUA	0.188	0.003
ApoB	0.195	0.002
TG		
SUA	0.216	0.001
HDL-C	−0.499	<0.001
ApoB	0.472	<0.001
MDA	0.128	0.043
UA		
Age	0.194	0.002
SystBP	0.178	0.005
ApoB	0.205	0.001
ApoB		
SystBP	0.158	0.013
DiastBP	0.171	0.007
HDL-C		
DiastBP	0.142	0.025
SUA	−0.179	0.005
ApoB	−0.204	0.001
MDA	−0.163	0.010
TG/HDL		
TC	0.125	0.050
SUA	0.221	<0.001
ApoB	0.433	<0.001
MDA	0.154	0.015
LDL-C		
ApoB	0.720	<0.001

Table 3 Association of elevated serum uric acid with (A) components of MetS, (B) MetS, (C) TG/HDL-C ratio and (D) increased oxidative stress after adjusting for their covariates in abdominal obesity subjects

Variables	Elevated uric acid		
	OR	95 % CI	P value
(A-1)			
^a Abdominal obesity	3.18	1.97–5.15	<0.001
SystBP	1.01	0.99–1.03	0.050
DiastBP	0.99	0.96–1.01	0.247
Age	1.02	0.99–1.04	0.104
Sex	0.89	0.55–1.47	0.665
(A-2)			
^a Elevated plasma Glu	2.62	2.29–5.36	0.002
SystBP	1.01	0.99–1.03	0.326
DiastBP	0.99	0.97–1.03	0.909
Age	1.02	0.99–1.04	0.269
Sex	0.55	0.31–0.96	0.036
(A-3)			
^a Elevated triglycerides	3.18	1.78–5.69	<0.001
SystBP	1.01	0.99–1.03	0.456
DiastBP	0.99	0.97–1.03	0.889
Age	1.02	0.99–1.05	0.128
Sex	0.45	0.26–0.80	0.006
(A-4)			
^a Reduced HDL-C	2.11	1.12–3.96	0.020
SystBP	1.01	0.99–1.03	0.220
DiastBP	0.99	0.97–1.03	0.813
Age	1.03	0.99–1.05	0.059
Sex	0.37	0.20–0.67	0.001
(A-5)			
^b Elevated TG/HDL-C ratio	2.19	1.36–3.51	0.001
WC	2.52	1.54–4.12	<0.001
SystBP	1.32	0.79–2.20	0.295
DiastBP	0.83	0.49–1.39	0.477
Age	1.02	1.00–1.04	0.042
Sex	0.97	0.59–1.60	0.910
(A-6)			
^c Metabolic syndrome	3.51	2.29–5.36	<0.001
Age	1.03	1.01–1.05	0.007
Sex	0.94	0.58–1.52	0.799
(B)			
^b Elevated oxidative stress	2.88	1.74–4.75	<0.001
SystBP	1.21	0.71–2.05	0.477
DiastBP	0.75	0.44–1.273	0.286
WC	1.02	0.99–1.05	0.067
Age	1.02	0.99–1.04	0.051
Sex	1.07	0.65–1.76	0.796

^a Model after adjusted with SystBP, DiastBP, Age and sex^b Model after adjusted with WC, SystBP, DiastBP, Age and sex^c Model after adjusted with Age and sex

3.51 (2.29, 5.36), and 2.88 (1.74, 4.75), respectively for these analysis, after adjusting for their covariates as shown in Table 3.

Discussion

Elevated SUA in human circulation carry an evolutionary advantage and it is a major antioxidant that protects cardiac, vascular, and neural cells from oxidative injury [20, 21]. Our finding demonstrated that SystBP, DiastBP, WC, BMI, Glu, SUA, TC, TG, LDL-C, ApoB and MDA were higher and HDL-C level was lower in AO subjects. In the present study also demonstrated elevated SUA is associated with elevated oxidative stress and the component of MetS after adjusted for their covariates by using multiple logistic regression analysis. Many studies have also suggested that increased oxidative stress is a feature of many risk factors for premature atherosclerosis, diabetes [22] and HT [23]. In a variety of organs and vascular beds, local UA concentrations increase during acute oxidative stress and ischemia, and the increased SUA concentrations might be a compensatory mechanism that confers protection against increased free radical activity [24]. Hyperuricemia even without crystal deposition and gout is strongly associated with cardiovascular disease, kidney disease, and HT increasing the risk of mortality [25]. Hyperuricemia is also common in the MetS and obesity [2, 13], Tsushima et al. [26] reported that adipose tissue could produce and secrete uric acid through xanthine oxidoreductase and that the production was enhanced in obesity by using mouse models. There is the tremendous complexity of these disorders, the common pathogenetic feature for all of them is paradoxically an involvement of oxidative stress and oxidative modifications of macromolecules including proteins and lipids as well as redox-dependent low-grade inflammation [9, 10, 27]. Oxidative stress and inflammation in the adipose tissue induce an imbalance in the production of adipocyte-specific hormones and cytokines (adipokines) that contribute substantially to the development of insulin resistance and cardiovascular risk associated with obesity [9, 10, 28, 31]. Fabbrini et al. [13] demonstrated that SUA is a major antioxidant and might help protect against free-radical oxidative damage in obese subjects. Schizophrenia is associated with a complex pathophysiology and outcome of radical mediated neurotoxicity. Dadheech et al. [29] demonstrated that the levels of endogenous antioxidants viz. GSH, bilirubin, total protein, albumin and uric acid, are disturbed in condition of schizophrenia which is an attempt to neutralize the ROS in body and reduce oxidative stress. These results to some extent support the role of endogenous antioxidants as components of total antioxidant response.

In the present study, we observed that higher levels of SUA were significantly associated with increasing BMI, waist circumference, blood pressure, serum levels of total cholesterol, LDL-C, and triglycerides. It has long been known that dyslipidemia, a high triglyceride, LDL-C, a low

HDL-C, and obesity are indicative of pro-inflammatory state/oxidative stress [30]. Concerning uric acid, in vitro studies suggest that uric acid has pro-inflammatory effects. Uric acid has been shown to stimulate production of monocyte chemoattractant protein-1 by vascular smooth muscle cells, interleukin-1 β , interleukin-6, and tumor necrosis factor- α by human mononuclear cells, C-reactive protein by cultured human vascular cells [30, 31]. SUA elevation may be a sensitive marker for underlying vascular inflammation. In fact, the present study demonstrated that elevated SUA was significantly associated with reduced HDL-C and elevated triglycerides, the both components risk of MetS in these subjects. These findings suggest the presence of a pro-inflammatory state in conjunction with impaired anti-inflammatory properties of HDL-C in the development of MetS, as reported in other populations [32, 33]. Given that pro-inflammatory state/oxidative stress often preceded or prominently involved in MetS [34], uric acid might contribute to the development of MetS through a pro-inflammatory pathway. AO is associated with increased oxidative stress and uric acid has potent counteracting antioxidant effects [2, 13].

We also demonstrated that elevated SUA associated with elevated TG/HDL-C ratio after adjusting with their covariates. This ratio has been identified as a reliable marker of insulin resistance in overweight, obese and T2DM patients [19, 20] and with the risk of cardiovascular events [35]. Although hyperuricemia is often considered as a compensatory mechanism in the MetS [27], it has also been noticed to be an independent predictor of obesity and hyperinsulinemia [3, 12, 13].

Obesity induced by a high-fat and/or high-carbohydrate leads to enhanced oxidative stress in rats [36]. Reactive oxygen species were also overproduced in rat model of MetS induced by a diet high in fat and refined sugar [37]. Oxidative stress is a common pathogenic factor for the dysfunction of endothelial cells and β -cells. Increased oxidative stress appears to be a deleterious factor leading to insulin resistance, β -cells dysfunction, impaired glucose tolerance, and ultimately T2DM [38]. Obesity may play a role in the relationship between systemic oxidative stress and all of these conditions [12, 13, 38]. These data from our community sample are consistent with others demonstrating that oxidative stress is a key pathway leading to insulin resistance and hyperuricemia. SUA is a major antioxidant and might help protect against free-radical oxidative damage.

Conclusion

Our study demonstrated that SUA may play a major role as an antioxidant and might help protect against free-radical

oxidative damage. SUA may be often associated with components of MetS, insulin resistance, MetS and oxidative stress. Then, SUA may be a marker of MetS, insulin resistance and increased oxidative stress, implying an increased risk of vascular disease and T2DM.

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Conflict of interest No conflict of interest.

References

1. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–52.
2. Yang T, Chu CH, Bai CH, You SL, Chou YC, Chou WY, Chien KL, Hwang LC, et al. Uric acid level as a risk marker for metabolic syndrome: a Chinese cohort study. *Atherosclerosis*. 2012;220:525–31.
3. Yoo TW, Sung KC, Shin HS, Yoo TW, Sung KC, Shin HS, et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J*. 2005;69:928–33.
4. Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH. Resurrection of uric acid as a causal risk factor in essential hypertension. *Hypertension*. 2005;45:18–20.
5. Coutinho TA, Turner ST, Peyser PA, et al. Associations of serum uric acid with markers of inflammation, metabolic syndrome and subclinical coronary atherosclerosis. *Am J Hypertens*. 2007;20:83–9.
6. Hiuge-Shimizu A, Kishida K, Funahashi T, Ishizaka Y, Oka R, Okada M, et al. Absolute value of visceral fat area measured on computed tomography scans and obesity-related cardiovascular risk factors in large-scale Japanese general population (the VACATION-J study). *Ann Med*. 2012;44:82–92.
7. Kishida K, Funahashi T, Shimomura I. Clinical importance of assessment of type 2 diabetes mellitus with visceral obesity. A Japanese perspective. *Curr Diabetes Rev*. 2012;8:84–91.
8. Keaney JF Jr, Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. *Arterioscler Thromb Vasc Biol*. 2003;23:434–9.
9. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004;114:1752–61.
10. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006;440:944–8.
11. Bielski BHJ. Reevaluation of the spectral and kinetic properties of HO₂ and O₂⁻ free radicals. *Photochem Photobiol*. 1978;28:645–9.
12. Singh RP, Sharad S, Kapur S. Free radicals and oxidative stress in neurodegenerative diseases: relevance of dietary antioxidants. *JACM*. 2004;5:218–25.
13. Fabbri E, Serafini M, Baric IC, Hazen SL, Klein S. Effect of plasma uric acid on antioxidant capacity, oxidative stress, and insulin sensitivity in obese subjects. *Diabetes*. 2014;63:976–81.
14. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006;23:469–80.
15. Nagahama K, Iseki K, Inoue T, Touma T, Ikemiya Y, Takishita S. Hyperuricemia and cardiovascular risk factor clustering in a screened cohort in Okinawa Japan. *Hypertens Res*. 2004;27:227–33.
16. Brehm A, Pfeiler G, Pacini G, Vierhapper H, Roden M. Relationship between serum lipoprotein ratios and insulin resistance in obesity. *Clin Chem*. 2004;50:2316–22.
17. Tangvarasittichai S, Poonsub P, Tangvarasittichai O. Association of serum lipoprotein ratios with insulin resistance in type 2 diabetes mellitus. *Indian J Med Res*. 2010;131:641–8.
18. Marcovina SM, Albers JJ, Dati F, Ledue TB, Ritchie RF. International Federation of Clinical Chemistry standardization project for measurements of apolipoproteins A-I and B. *Clin Chem*. 1991;37:1676–82.
19. Tangvarasittichai S, Poonsub P, Tangvarasittichai O, Sirigulsatien V. Serum levels of malondialdehyde in type 2 diabetes mellitus Thai subjects. *Siriraj Med J*. 2009;61:20–3.
20. Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA. Uric acid and oxidative stress. *Curr Pharm Des*. 2005;11:4145–51.
21. Stocker R, Keaney JF Jr. Role of oxidative modifications in atherosclerosis. *Physiol Rev*. 2004;84:1381–478.
22. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006;440:944–8.
23. Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res*. 2000;86:494–501.
24. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? *Atherosclerosis*. 2000;148:131–9.
25. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*. 2003;41:1183–90.
26. Tsumura Y, Nishizawa H, Tochino Y, Nakatsuji H, Sekimoto R, Nagao H, et al. Uric acid secretion from adipose tissue and its increase in obesity. *J Biol Chem*. 2013;288:27138–49.
27. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest*. 2005;115:1111–9.
28. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res*. 2005;96:939–49.
29. Dadheech G, Sharma P, Gautam S. Oxidative stress-induced response of some endogenous antioxidants in Schizophrenia. *Ind J Clin Biochem*. 2012;27:278–83.
30. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol*. 2005;25:39–42.
31. Gagliardi ACM, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. *Atherosclerosis*. 2009;202:11–7.
32. Onat A, Can G, Ayhan E, Kaya Z, Hergenc G. Impaired protection against diabetes and coronary heart disease by high-density lipoproteins in Turks. *Metabolism*. 2009;58:1393–9.
33. Tohidi M, Hatami M, Hadaegh F, Safarkhani M, Harati H, Azizi F. Lipid measures for prediction of incident cardiovascular disease in diabetic and non-diabetic adults: results of the 8.6 years of follow-up of a population based cohort study. *Lipids Health Dis*. 2010;9:6.
34. Onat A. Metabolic syndrome: nature, therapeutic solutions and options. *Expert Opin Pharmacother*. 2011;12:1887–900.
35. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Low triglycerides-high density lipoprotein cholesterol and risk of ischemic heart disease. *Arch Intern Med*. 2001;161:361–6.

36. Dobrian AD, Davies MJ, Schriver SD, Lauterio TJ, Prewitt RL. Oxidative stress in a rat model of obesity-induced hypertension. *Hypertension*. 2001;37:554–60.
37. Roberts CK, Barnard RJ, Sindhu RK, Jurczak M, Ehdaie A, Vaziri ND. Oxidative stress and dysregulation of NAD(P)H oxidase and antioxidant enzymes in diet-induced metabolic syndrome. *Metabolism*. 2006;55:928–34.
38. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Are oxidative stress-activated signaling pathways mediators of insulin resistance and β -cell dysfunction? *Diabetes*. 2003;52:1–8.