Research Article

Hui-Juan Wang, Lei-Zhi Shi, Cun-Fei Liu, Shi-Min Liu, Song-Tao Shi*

Association between uric acid and metabolic syndrome in elderly women

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Abstract: Objective. To investigate the relationship between uric acid and metabolic syndrome (MetS) in elderly women.

Methods. A total of 468 women aged ≥60 years participating in a health examination were enrolled. The association between uric acid and MetS and its individual variables was evaluated by univariate and multivariate logistic regression models.

Results. A dose-response relationship was observed for the prevalence of MetS and uric acid quartiles. Subjects in the second, third and fourth quartile of uric acid had a 2.23-fold, 2.25-fold and 4.41-fold increased risk, respectively, of MetS than those in the first uric acid quartile (p for trend <0.001). Furthermore, each 1 mg/dl increment of serum uric acid level had a 1.38-fold increased risk of MetS (OR 1.38; 95% CI, 1.14-1.69; p=0.001).

Conclusions. Our present study demonstrated that elevated uric acid was positively associated with the prevalence of MetS in elderly women. Further random control trials are needed to elucidate the effectiveness of treatment of hyperuricaemia in reducing the incidence of MetS in elderly women.

Keywords: Uric acid; Metabolic syndrome; Elderly women

***Corresponding author: Song-Tao Shi,** Department of Thoracic Surgery, Linyi People's Hospital, Linyi, Shandong, 276000, China, Fax: +86-0539-8090319, E-mail: shist62@163.com
Hui-Juan Wang, Lei-Zhi Shi, Department of Thoracic Surgery, Linyi People's Hospital, Linyi, Shandong, 276000, China
Cun-Fei Liu, Department of Cardiology, Linyi People's Hospital, Linyi, Shandong, 276000, China
Shi-Min Liu, Department of Internal Medicine, Linyi People's Hospital, Linyi, Shandong, 276000, China

1 Introduction

Metabolic syndrome (MetS) consists of a range of risk factors including obesity, hyperglycaemia, high blood pressure, high triglycerides, and low high-density lipoprotein cholesterol [1]. MetS is associated with increased risk of type 2 diabetes mellitus (DM), cardiovascular disease, cardiovascular mortality and all-cause mortality [2, 3], and is regarded as a critical public health and clinical challenge given its high prevalence in developing and developed countries [4, 5]. Hence, detection and intervention against MetS as early as possible are necessary for preventing the progression of MetS related diseases and reducing the public health burden in the world.

Uric acid (UA) is the end product of purine metabolism in humans[6]. Recent studies have demonstrated that elevated UA may be a predictor for MetS in different populations [7-10]. However, results of these studies are controversial, and research on the relationship between UA and MetS in elderly populations is insufficient. The prevalence of MetS is much higher in elderly populations, especially in women [11, 12], and previous studies showed that MetS was associated with higher cardiovascular risk in women than men [13, 14]. Therefore, we conducted a cross-sectional study to investigate the relationship between UA and MetS and its components in elderly women.

2 Methods

2.1 Subjects

Our present study enrolled 468 Han Chinese elderly women (aged 60-90 years) who visited for an annual health examination in Linyi People's Hospital from March 2016 to October 2016. All subjects completed a physical check-up according to a standardized protocol. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of Linyi People's Hospital and was conducted in accordance with the guidelines of the Helsinki Declaration.

2.2 Data collection and laboratory measurement

Trained nurses administered standardized questionnaires to obtain general information, including age, past illness history, history of drug treatment, smoking, drinking, etc. Height was measured without shoes by calibrated height metres, and weight was measured to the nearest 0.1 kg. Waist circumference (WC) was measured between the iliac crest and rib cage with a non-elastic tape. Body mass index (BMI) was evaluated by the formula weight (kg)/height^2 (m^2). Blood pressure was measured 3 times with an automated sphygmomanometer in the seated position after at least 5 minutes of rest.

Venous blood samples after overnight fasting were obtained from the antecubital vein and were then sent to the hospital laboratory for analysis. Laboratory parameters, including fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), creatinine, UA and liver function index (Alanine aminotransferase, Aspartate transaminase) were measured enzymatically on an automatic analyser (Architect Ci8200, Abbott Co., Illinois, USA). All laboratory assessments were performed by trained clinical laboratory technicians, according to the standard operating procedures of the hospital laboratory.

2.3 Definition of MetS

We used the 2009 harmonizing definition criteria of MetS[15]: central obesity: WC≥ 80 cm in Asian women; high blood pressure: systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, or use of antihypertensive drugs; high TG: TG ≥150 mg/dl; low HDL-C: HDL-C<50 mg/dl in women; and hyperglycaemia: FPG ≥100 mg/dl or use of antidiabetic agents.

2.4 Statistical analysis

Continuous variables are described as the mean with standard deviation (SD), and Student's t-test or one-way ANOVA was used to compare the difference in characteristics between the two groups or multiple groups. Categorical variables were summarized as numbers and percentages and were compared using the chi-square test. Univariate and multivariate logistic regression analyses were performed to evaluate the crude and adjusted ORs for MetS and its components according UA quartile. All statistical tests were two-sided, and p-value <0.05 was considered significant. All statistical analyses were conducted using SPSS software 18.0 (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Differences in characteristics between the MetS and Non-MetS groups

A total of 468 female subjects were enrolled in our present study, and the main characteristics are shown in Table 1. Among these, 161 subjects were diagnosed with MetS

Table 1: Characteristics of the study populations

	MetS (n=161)	Non-MetS (n=307)	P value
Age (year)	69.34±7.11	70.60±6.76	0.065
BMI (kg/m^2)	26.37±3.08	22.85±2.52	<0.001
WC (cm)	84.39±9.85	73.12±8.05	<0.001
HBP	124(77.0%)	124(40.4%)	<0.001
DM	54(33.5%)	37(12.1%)	<0.001
SBP (mmHg)	139.32±15.12	131.24±17.26	<0.001
DBP (mmHg)	79.27±9.59	77.10±9.82	0.023
TG (mg/dl)	239.13±131.57	139.54±86.58	<0.001
TC (mg/dl)	216.12±47.35	206.14±38.62	0.015
HDL-C (mg/dl)	62.06±17.86	74.14±18.54	<0.001
LDL-C (mg/dl)	110.85±36.16	103.14±29.16	0.013
FPG (mmol/L)	6.47±2.20	5.40±1.25	<0.001
ALT (IU/L)	24.77±14.58	21.64±14.17	0.025
AST (IU/L)	24.62±14.58	24.19±8.80	0.634
Uric acid (mg/dl)	5.72±1.49	5.03±1.28	<0.001
Creatinine (mg/dl)	0.74±0.18	0.74±0.17	0.905
eGFR	77.09±27.29	76.63±23.37	0.849
No of MetS components	3.36±0.48	1.36±0.68	<0.001

Abbreviations: BMI: body mass index; WC: waist circumference; TG: triglyceride;

TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate.

according to the criteria, and the overall incidence of MetS was 34.4%. There was no significant difference in mean age (69.34 years vs 70.60 years, p=0.065), AST (24.62 IU/L vs 24.19 IU/L, p=0.634) or creatinine level (5.72 mg/dl vs 5.04 mg/dl, p=0.897) between the MetS and non-MetS groups. Compared with the non-MetS group, there was a significantly higher prevalence of hypertension (77.0% vs 40.4%, p<0.001) and DM (33.5% vs 12.1%, p<0.001) in the MetS group. Additionally, subjects in the MetS group had significantly greater BMI and WC, higher levels of SBP, TG, TC, LDL –C, FPG, ALT, and uric acid, and a greater number of MetS components (all p values <0.05 or 0.01). In contrast, the MetS group had significantly lower levels of HDL-C than the non-MetS group (62.06 mg/dl vs 74.14 mg/dl, p< 0.001).

3.2 Subject characteristics according to uric acid quartiles

We next evaluated general subject characteristics according to uric acid quartile (Table 2). The subjects were categorized into 4 groups based on the following uric acid cut-off values: Q1: ≤4.26, Q2: 4.26-5.12, Q3: 5.12-6.11, and Q4: >6.11. The prevalence of MetS (p for trend <0.001) and hypertension (p for trend =0.017) was significantly increased with the increment of uric acid quartile. Additionally, significantly increased levels of age, BMI, WC, TG, ALT and creatinine were found across uric acid quartiles (all p values for trend <0.05). However, there was no substantial difference in the prevalence of DM, SBP, DBP, TC, LDL-C, FPG, AST across uric acid quartiles (all p values for trend>0.05).

Table 2: Characteristics of subjects according to quartiles of UA

	Q1 (n=117)	Q2 (n=117)	Q3 (n=117)	Q4 (n=117)	P value
UA quartiles (mg/dl)	≤4.26	4.26-5.12	5.12-6.11	>6.11	
Age (year)	69.21±7.33	69.06±6.66	69.46±7.03	71.37±6.86	0.041
BMI (kg/m2)	23.14±3.19	23.80±2.98	23.99±2.85	25.32±3.36	<0.001
WC (cm)	74.06±10.23	76.17±9.53	76.76±9.13	81.02±10.76	<0.001
HBP	52(44.4%)	57(48.7%)	64(54.7%)	75(64.1%)	0.017
DM	22(18.8%)	19(16.2%)	25(21.4%)	25(21.4%)	0.717
SBP (mmHg)	134.01±17.92	134.79±18.70	133.21±15.49	134.08±15.75	0.917
DBP (mmHg)	78.25±10.28	77.50±10.53	78.44±8.71	77.19±9.58	0.381
TG (mg/dl)	137.59±89.28	162.48±94.46	160.59±85.61	234.53±152.03	<0.001
TC (mg/dl)	204.95±35.12	209.38±43.05	206.60±36.87	217.35±50.78	0.111
HDL-C (mg/dl)	78.39±22.38	70.86±18.53	67.26±17.37	63.43±14.52	<0.001
LDL-C (mg/dl)	100.18±27.34	106.59±32.48	104.81±29.71	111.58±36.71	0.053
FPG (mmol/L)	5.95±2.54	5.54±1.07	5.79±1.49	5.78±1.38	0.329
ALT (IU/L)	21.92±13.62	20.07±10.64	22.97±13.94	25.90±17.91	0.017
AST (IU/L)	23.96±10.32	23.03±7.30	24.20±7.85	26.16±10.57	0.064
Creatinine (mg/dl)	0.67±0.16	0.71±0.14	0.73±0.16	0.84±0.19	<0.001
eGFR	84.93±22.90	79.52±25.57	77.95±27.59	64.76±17.53	<0.001
MetS	22(18.8%)	37(31.6%)	38(32.5%)	64(54.7%)	<0.001
No of MetS components	1.68±0.99	1.89±1.20	2.10±1.07	2.53±1.09	<0.001

Abbreviations: BMI: body mass index; WC: waist circumference; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase. eGFR: estimated glomerular filtration rate.

3.3 Association between uric acid and the prevalence of MetS

Univariate and multivariate logistic regression analyses were performed to evaluate the association between MetS and uric acid quartile. The detailed results are shown in Table 3. The unadjusted OR for MetS increased from 1.99 (95% CI, 1.09–3.66) for the second quartile to 5.21 (95% CI, 2.89–9.40) for the fourth quartile (p for trend <0.001). In the multivariate logistic analysis, subjects in the second, third and fourth uric acid quartiles had a 2.23-fold, 2.25-fold and 4.41-fold increased risk, respectively, of MetS than those in the first uric acid quartile (p for trend <0.001). Furthermore, each 1 mg/dl increment of serum uric acid level had a 1.38-fold increased risk of MetS (OR, 1.38; 95% CI, 1.14–1.69; p=0.001). One previous study showed that the positive association between acid uric and MetS diminished with age in elderly people[16], and we obtained similar results in our present study: the ORs for MetS in the young old (60-74 years), old (75-84 years) and oldest old (85-94 years) were 1.52, 1.30, and 2.34, respectively, per 1 mg/dl increment of uric acid (detailed results are shown in supplementary material).

3.4 Association between uric acid and the incidence of individual MetS components

We further assessed the association between uric acid and individual MetS components. After adjustment for age, positive associations for uric acid quartile and individual MetS risk components were found for all components, except for hypertensive subjects (Table 4).

4 Discussion

The incidence of MetS significantly increases with increasing age. Li *et al.* [11] performed a meta-analysis including 226,653 Chinese subjects and showed that the prevalence of MetS was 32.4% in subjects ≥60 years old in Mainland China, which is significantly higher than that in populations of subjects less than 60 years old. Moreover, the authors also showed that MetS was more common in post-menopausal females than in elderly males (42.9 vs. 23.0 %). In this study, we investigated the association between uric acid and risk of MetS in elderly women. Our results showed that elevated uric acid was positively associated with MetS and its individual variables in elderly women; compared with subjects in the bottom quartile, the unadjusted MetS OR was 5.21 (95%CI 2.89–9.40) for the highest quartile group. The OR in the fourth quartile was still 4.41-fold higher than that in the first quartile after adjusting for several confounding factors. As to MetS components, our study suggested that uric acid was significantly correlated with central obesity, high TG and low HDL-C, but not with hypertension or hyperglycaemia.

A large number of epidemiological studies have found a positive relationship between serum uric acid levels and the prevalence of MetS. However, it is still controversial whether elevated uric acid levels are a risk factor or just a biomarker in the development and progression of MetS [17, 18]. Recent clinical and animal studies indicated that elevated uric acid levels might play a pathogenic role in the development of MetS [19]. Basic research has confirmed a causal role of uric acid in the onset of MetS and the benefits of lowering uric acid levels in preventing or reversing MetS [9,20,21]. A small randomized, controlled clinical trial has also verified the protective effect of lowering uric acid levels in the development of MetS [22]. The

Table 3: Odds ratios (95% CIs) of MetS according to quartiles of UA

	Q1 (n=117)	Q2 (n=117)	Q3 (n=117)	Q4 (n=117)	P for trend
UA quartiles (mg/dl)	≤4.26	4.26-5.12	5.12-6.11	>6.11	
Case	22	37	38	64	
Model 1	1	1.99(1.09-3.66)	2.08(1.14-3.80)	5.21(2.89-9.40)	<0.001
Model 2	1	2.01(1.10-3.68)	2.07(1.13-3.80)	5.05(2.79-9.13)	<0.001
Model 3	1	2.23(1.08-4.60)	2.25(1.09-4.66)	4.41(2.03-9.56)	<0.001
Per 1mg/dl UA increment	1.38(1.14-1.69)				0.001

Model 1: unadjusted OR.
Model 2: adjusted for age.
Model 3: adjusted for age, BMI, ALT, TC, LDL-C, Creatinine.

Table 4: Age-adjusted odds ratios of each individual MetS components according to quartiles of UA

	Q1 n=117	Q2 n=117	Q3 n=117	Q4 n=117	P for trend
UA quartiles (mg/dl)	≤4.26	4.26-5.12	5.12-6.11	>6.11	
Central obesity					
Case	30	37	40	60	
Odds ratio	1	1.34(0.76-2.37)	1.52(0.86-2.67)	3.21(1.84-5.61)	<0.001
High blood pressure					
Case	88	82	95	98	
Odds ratio	1	0.76(0.42-1.38)	1.41(0.74-2.67)	1.45(0.75-2.82)	0.102
Hyperglycemia					
Case	43	48	57	59	
Odds ratio	1	1.20(0.71-2.04)	1.63(0.97-2.75)	1.68(0.99-2.84)	0.028
High TG					
Case	33	53	53	79	
Odds ratio	1	2.11(1.22-3.63)	2.12(1.23-3.65)	5.48(3.12-9.62)	<0.001
Low HDL-C					
Case	4	8	11	18	
Odds ratio	1	2.01(0.61-7.19)	2.92(0.90-9.48)	4.83(1.57-14.80)	0.002

potential mechanisms of uric acid in inducing MetS are as follows: First, hyperuricaemia has been shown to induce endothelial dysfunction in both animal and human models [23,24]. Endothelial dysfunction is a hallmark of MetS [25]. Second, uric acid has been shown to inhibit the production and bioavailability of NO [26], which is essential for insulin action [27,28]. Thus, hyperuricaemia could induce or worsen insulin resistance by itself. Indeed, epidemiological studies have shown the predictive value of uric acid in the risk of insulin resistance [29]. In turn, insulin resistance is thought to play a pivotal role in MetS [30]. Additionally, despite being a classic antioxidant, uric acid can promote oxidative stress once inside the cell [31, 32]. Hyperuricaemia is also associated with elevated circulating levels of inflammatory cytokines, such as monocyte chemoattractant protein 1, C-reactive protein and tumour necrosis factor-α [26,33,34].

Our present study has several limitations. First, our study design is cross-sectional and we cannot draw a causal relationship between uric acid and MetS in elderly women. Second, the sample size in our study is not large enough. Moreover, we adjusted for several possible confounding factors in exploring the association of uric acid and MetS in our statistical analysis; however, residual confounding effects may still exist. For example, caloric intake, sodium intake, and exercise, etc., were not included in our study, which might lead to potential bias in the results.

In summary, our present study demonstrated that elevated uric acid was positively associated with the prevalence of MetS in elderly women. Further random control trials are needed to elucidate the effectiveness of treatment for hyperuricaemia in reducing the incidence of MetS in elderly women.

Conflicts of interest: The authors have no conflicts of interest to declare.

References

[1] Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab. 2007;92(2):399-404

[2] Thomas GN, Schooling CM, McGhee SM, Ho SY, Cheung BM, Wat NM. et al. Metabolic syndrome increases all-cause and vascular mortality: the Hong Kong Cardiovascular Risk Factor Study. Clin Endocrinol (Oxf). 2007;66(5):666-671

[3] Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112(20):3066-3072

[4] Gu D, Reynolds K, Wu X, Chen J, Duan X, Reynolds RF. et al. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet. 2005;365(9468):1398-1405
[5] Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes. 2010;2(3):180-193
[6] Wu XW, Muzny DM, Lee CC, Caskey CT. Two independent mutational events in the loss of urate oxidase during hominoid evolution. J Mol Evol. 1992;34(1):78-84
[7] Lee JK, Ryoo JH, Choi JM, Park SK. Serum uric acid level and the incidence of metabolic syndrome in middle-aged Korean men: a 5-year follow-up study. J Prev Med Public Health. 2014;47(6):317-326
[8] Nagahama K, Inoue T, Kohagura K, Ishihara A, Kinjo K, Ohya Y. Hyperuricemia predicts future metabolic syndrome: a 4-year follow-up study of a large screened cohort in Okinawa, Japan. Hypertens Res. 2013;37(3):232-238
[9] Wang J-Y, Chen Y-L, Hsu C-H, Tang S-H, Wu C-Z, Pei D. Predictive value of serum uric acid levels for the diagnosis of metabolic syndrome in adolescents. J Pediatr. 2012;161(4):753-756
[10] Ryu S, Song J, Choi B-Y, Lee S-J, Kim WS, Chang Y. et al. Incidence and risk factors for metabolic syndrome in Korean male workers, ages 30 to 39. Ann Epidemiol. 2007;17(4):245-252
[11] Li R, Li W, Lun Z, Zhang H, Sun Z, Kanu JS. et al. Prevalence of metabolic syndrome in Mainland China: a meta-analysis of published studies. BMC Public Health. 2016; 16(1): 296
[12] Liu M, He Y, Wu L, Wang J, Yang S, Wang Y. et al. [Association between metabolic syndrome and chronic kidney disease and sex specific difference among community elder population in Beijing]. Zhonghua Liu Xing Bing Xue Za Zhi. 2015;36(5):411-415
[13] Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK. et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49(4):403-414
[14] Santilli F, D'Ardes D, Guagnano MT, Davi G. Metabolic Syndrome: Sex-Related Cardiovascular Risk and Therapeutic Approach. Curr Med Chem. 2017;24(24):2602-2627
[15] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA. 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
[16] Chen JH, Hsieh CH, Liu JS, Chuang TJ, Chang HW, Huang CL. et al. The Power of Serum Uric Acid in Predicting Metabolic Syndrome Diminishes With Age in an Elderly Chinese Population. J Nutr Health Aging. 2016;20(9):912-917
[17] Soltani Z, Rasheed K, Kapusta DR, Reisin E. Potential role of uric acid in metabolic syndrome, hypertension, kidney injury, and cardiovascular diseases: is it time for reappraisal? Curr Hypertens Rep. 2013;15(3):175-181
[18] Borges RL, Ribeiro AB, Zanella MT, Batista MC. Uric acid as a factor in the metabolic syndrome. Curr Hypertens Rep. 2010;12(2):113-119
[19] Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, Rivard C. et al. Uric acid in metabolic syndrome: From an innocent bystander to a central player. Eur J Intern Med. 2016;29(4):3-8
[20] Reungjui S, Roncal CA, Mu W, Srinivas TR, Sirivongs D, Johnson RJ. et al. Thiazide diuretics exacerbate fructose-induced metabolic syndrome. J Am Soc Nephrol. 2007;18(10):2724-2731
[21] Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O. et al. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol. 2006;290(3):F625-F631
[22] Perez-Pozo S, Schold J, Nakagawa T, Sanchez-Lozada L, Johnson R, Lillo JL. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes. 2010;34(3):454-461
[23] Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W. et al. Hyperuricemia induces endothelial dysfunction. Kidney Int. 2005;67(5):1739-1742
[24] Mercuro G, Vitale C, Cerquetani E, Zoncu S, Deidda M, Fini M. et al. Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk. Am J Cardiol. 2004;94(7):932-935
[25] Deedwania PC. Mechanisms of endothelial dysfunction in the metabolic syndrome. Curr Diab Rep. 2003;3(4):289-292
[26] Kang D-H, Park S-K, Lee I-K, Johnson RJ. Uric acid–induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol. 2005;16(12):3553-3562
[27] Wu G, Meininger CJ. Nitric oxide and vascular insulin resistance. Biofactors. 2009;35(1):21-27.
[28] Roy D, Perreault M, Marette A. Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues in vivo is NO dependent. Am J Physiol Endocrinol Metab. 1998;274(4):E692-E699
[29] Krishnan E, Pandya BJ, Chung L, Hariri A, Dabbous O. Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: a 15-year follow-up study. Am J Epidemiol. 2012;176(2):108-116
[30] Lann D, LeRoith D. Insulin resistance as the underlying cause for the metabolic syndrome. Med Clin N Am. 2007;91(6):1063-1077
[31] Schorn C, Janko C, Munoz L, Schulze C, Strysio M, Schett G. et al. Sodium and potassium urate crystals differ in their inflammatory potential. Autoimmunity. 2009;42(4):314-316
[32] Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol. 2007;293(2):C584-C596
[33] Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T. et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension. 2003;41(6):1287-1293
[34] di Giovine FS, Malawista SE, Thornton E, Duff GW. Urate crystals stimulate production of tumor necrosis factor alpha from human blood monocytes and synovial cells. Cytokine mRNA and protein kinetics, and cellular distribution. J Clin Invest. 1991;87(4):1375-1381