Original Article

JHSMR Journal of Health Science and Medical Research

Associations and Combinations of Metabolic Parameters and *ABCG2* rs2231142 Variant in Thai Men with Gout

Kitsarawut Khuancharee, Ph.D.[1], Chantra Tanunyutthawongse, M.D.[2], Chawin Suwanchatchai, M.D.[3], Sivaporn Wannaiampikul, Ph.D.[4]

[1]Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhon Nayok 26120, Thailand.

[2]Department of Biochemistry, Faculty of Medicine, Srinakharinwirot University, Watthana, Bangkok 10110, Thailand.

[3]Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhon Nayok 26120, Thailand.

[4]Department of Biochemistry, Faculty of Medicine, Srinakharinwirot University, Watthana, Bangkok 10110, Thailand.

Received 24 July 2022 ● Revised 31 October 2022 ● Accepted 2 November 2022 ● Published online 17 January 2023

Abstract:

Objective: This study aimed to investigate whether the risk of gout was associated with the *ABCG2* rs2231142 variant and how this was affected by metabolic parameters.

Material and Methods: The subjects were selected from the genetic variations of urate transporter genes in hyperuricemia and gout in the Thai population (GUHGTH) study. Overall, 96 participants aged 30–60 years were included in the study. Adjusted odds ratio (AORs) of gout was analyzed using multiple logistic regression models and the effects of combinations of *ABCG2* rs2231142 variants and metabolic parameters on gout were explored.

Results: The TG and TT genotypes of ABCG2 rs2231142 and hyperglycemia were significantly associated with gout risk. The risk of gout was significantly increased by the combined association of *ABCG2* rs2231142 and metabolic parameters obesity and hyperglycemia for the TG and TT genotypes compared to the GG genotype (wild-type genotype).

Conclusion: In conclusion, the *ABCG2* rs2231142 variant was found to be a genetic risk factor for gout in Thai men. Obesity and hyperglycemia combined with the *ABCG2* rs2231142 risk allele contributed to an increase in the risk of gout. Further case-control studies with larger sample sizes should be performed to confirm the combinations of the *ABCG2* rs2231142 variant, obesity, and hyperglycemia on the risk of gout.

Keywords: *ABCG2* rs2231142 variant, combinations, gout, men, metabolic parameters

Contact: Sivaporn Wannaiampikul, Ph.D.
Department of Biochemistry, Faculty of Medicine, Srinakharinwirot University, Watthana, Bangkok 10110, Thailand.
E-mail: siblossom@hotmail.com

J Health Sci Med Res 2023;41(3):e2023923
doi: 10.31584/jhsmr.2023923
www.jhsmr.org

Introduction

Gout, which is the most common form of inflammatory arthritis[1], is caused by the deposition of monosodium urate crystals in and around the joints[2]. Several studies have reported that the prevalence rate of gout is increasing rapidly in various populations[1,3–6]. Epidemiological research has reported that men have higher serum uric acid levels and gout risk than women[7]. Epidemiological studies have found that socioeconomic factors[4], dietary factors[1,4,8–10], and genetic factors[4] are important in determining the risk of gout. Additionally, metabolic syndrome parameters (e.g., obesity[11], hypertension[10,12], insulin resistance[13,14], and dyslipidemia[15–18]) have also been related to gout. The previous genome-wide association studies demonstrated that genetic variations in the ATP-binding cassette, subfamily G, member 2 (*ABCG2*) were strongly related to hyperuricemia (HUA) and an increased risk of gout[19]. The *ABCG2* rs2231142 variant is a high-capacity urate transporter that excretes uric acid[20]. The *ABCG2* rs2231142 variant is more strongly associated with both HUA and gout in the Asian population compared to the European population[21–27]. These various findings indicate that the *ABCG2* rs2231142 variant may have specific and essential functions in the pathology of patients with gout[20]. However, an association between the *ABCG2* rs2231142 variant and gout has not been studied in Thai men. Therefore, this study was undertaken to study the association between gout and the *ABCG2* rs2231142 variant and how this is affected by metabolic parameters in Thai men.

Material and Methods

Data source and study population

A matched case-control study was performed using the GUHGTH study (approval number MEDSWUEC-148/60E). The participants enrolled in the study were Thai men aged 18–80 years with and without gout. All 77 gout cases had been diagnosed with gout according to the Rome criteria[28] at the HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC), Nakhon Nayok, Thailand. As a comparative group, 68 subjects without a history of gout and hyperuricemia were also enrolled. We randomly matched gout-free controls according to age (±10 years) to the gout patients. The exclusion criteria included an age mismatch and genotyping quality control failure. The subjects with cardiovascular disease, kidney disease or kidney dysfunction, cancer, stress and anxiety, and drug-induced hyperuricemia and gout were also excluded. Finally, a total of 96 subjects (48 who had gout and 48 control subjects) were matched and included in the study.

Measurement of genotyping, clinical, and biochemical data

Genotyping information, demographic information, physical examination results (body mass index (BMI) and blood pressure (BP, mmHg)), and biochemical reports including total cholesterol (TC), triglycerides (TG), high- and low-density lipoprotein cholesterol (HDL-C and LDL-C), fasting plasma glucose (FPG), and serum uric acid (SUA), were collected from the GUHGTH study. The DNA blood samples from the GUHGTH study participants were genotyped using TaqMan SNP Genotyping Assays (Applied Biosystems, USA) to detect single nucleotide polymorphisms (SNPs), particularly, the rs2231142 variant of the *ABCG2* gene. All available data were achieved from the GUHGTH study, which collected specimens and information in a complete and standardized procedure to fit researchers' needs in the study.

BMI was measured by dividing the weight in kilograms (kg) by the height in meters squared (m^2). Obesity was defined as BMI ≥23 kg/m^2. Hypertension was defined as BP ≥130/85 mmHg or being on medicine to treat high BP. Hyperlipidemia was defined as TC ≥ 200 mg/dL, TG ≥ 150 mg/dL, and HDL <40 mg/dL in men or <50 mg/dL in women or being on medication. Suspected diabetes mellitus was defined as FPG ≥100 mg/dL or being on medication.

Statistical analysis

The collected data were analyzed using STATA version 14. Descriptive statistics were used for all variables. Genotype and allele distributions for polymorphisms were determined by the Hardy–Weinberg equilibrium using SNPStats (https://www.snpstats.net/start.htm). Adjusted odds ratios (AORs) and their 95% confidence interval (95% CIs) of metabolic parameters (obesity and lipid profile) and *ABCG2* rs2231142 variant on gout were calculated by a multiple conditional logistic regression model. Multiple logistic regression models were also used for evaluating the effect of combinations of *ABCG2* rs2231142 and metabolic parameters on gout. Genetic associations between the *ABCG2* rs2231142 genotypes and gout were analyzed using dominance analysis. The statistical significance was set at p-values of less than 0.05.

Results

A total of 96 subjects were recruited and matched in the study. As shown in Table 1, the characteristics of the subjects, including age, BMI, diastolic BP, TG, HDL-C, FPG, LDL-C, and SUA, were not significantly different between the gout cases and the control subjects. However, the systolic blood pressure in the gout cases was higher than that in the controls, and total cholesterol was lower. The *ABCG2* rs2231142 genotype frequencies among the gout cases were 21.0% (TT), 52.0% (TG), and 27.0% (GG), while the *ABCG2* rs2231142 genotype frequencies in the control subjects were 2.0% (TT), 33.0% (TG), and 65.0% (GG). The distribution of the minor *ABCG2* rs2231142 T allele was 47.0% of the gout cases compared with 19.0% of the control subjects (Table 2).

Multivariate analysis found that the number of subjects who carried the mutant *ABCG2* rs2231142 (TG-TT) variant and had hyperglycemia was significantly higher in the gout cases (Table 3). As shown in Table 4, the risk of gout was increased by the combinations of the *ABCG2* rs2231142 TG-TT genotypes and obesity. Our study also found that the combinations of the *ABCG2* rs2231142 TG-TT genotypes and hyperglycemia were associated with gout in Thai men. We also found that obese subjects carrying the *ABCG2* rs2231142 TG-TT genotypes had a higher risk of gout than nonobese subjects carrying the *ABCG2* rs2231142 TG-TT genotypes. Also, hyperglycemia subjects carrying the *ABCG2* rs2231142 TG-TT genotypes had a higher risk of gout than those subjects with normal

Table 1 Anthropometric and laboratory findings of study subjects

Parameter	Gout (n=48) Mean±(S.D.)	Non-gout (n=48) Mean±(S.D.)
Age (years)	57.94±(12.23)	54.58±(14.64)
BMI (kg/m^2)	26.20±(5.00)	24.95±(3.58)
SBP (mmHg)	141.42±(17.74)	131.67±(12.22)
DBP (mmHg)	83.21±(11.68)	81.92±(10.04)
Total cholesterol (mg/dL)	186.67±(56.92)	202.27±(41.88)
Triglycerides (mg/dL)	166.04±(64.19)	145.89±(81.80)
HDL-C (mg/dL)	50.79±(23.73)	54.14±(10.62)
LDL-C (mg/dL)	101.57±(49.19)	121.21±(37.35)
FPG (mg/dL)	108.06±(18.82)	110.77±(48.43)
SUA levels (mg/dL)	6.28±(2.27)	6.47±(1.19)

BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, FPG=fasting plasma glucose, SUA=serum uric acid, S.D.=standard deviation

FPG carrying the *ABCG2* rs2231142 TG–TT genotypes. In contrast, no significant combinations which were associated with gout were found between the *ABCG2* rs2231142 TG–TT genotypes and high TG, low HDL–C, and high BP.

Table 2 Genotype and allele distributions of study subjects

SNPs	Genotype or allele	Gout (n=48), n (%)	Non-gout (n=48), n (%)	p-value for HWE*
ABCG2-rs2231142				
	G/G	13 (27.0)	31 (65.0)	0.820
	G/T	25 (52.0)	16 (33.0)	
	T/T	10 (21.0)	1 (2.0)	
	G/T–T/T	35 (73.0)	17 (35.0)	
	Allele, G (%)	51 (53.0)	78 (81.0)	
	Allele, T (%)	45 (47.0)	18 (19.0)	

HWE=Hardy–Weinberg equilibrium test, SNPs=single-nucleotide polymorphisms
*Chi-square test

Table 3 Associations between *ABCG2* rs2231142 and metabolic parameters in gout in study subjects

Factor	OR	95% CI	AOR	95% CI
rs2231142				
G/G	1.00			
G/T–T/T	3.57	1.54–8.26	3.53	1.16–10.71
Body mass index (BMI)				
Normal	1.00			
High (≥23 kg/m^2)	1.80	0.83–3.90	1.95	0.77–4.89
Fasting plasma glucose (FPG)				
Normal	1.00			
High (≥100 mg/dL)	5.00	1.71–14.63	3.86	1.27–14.50
Triglycerides (TG)				
Normal	1.00			
High (≥150 mg/dL)	1.89	0.84–4.24	1.31	0.48–3.62
High-density lipoprotein cholesterol (HDL-C)				
Normal	1.00			
Low	0.57	0.17–1.95	0.62	0.15–2.50
Blood pressure(BP)				
Normal	1.00			
High (≥130/85 mmHg)	1.04	0.87–1.19	1.31	0.89–1.62

CI=confidence interval, OR=odds ratio, AOR=adjusted odds ratio using a multiple conditional logistic regression model

Table 4 Combinations of metabolic parameters and *ABCG2* rs2231142 variant

Genotype	Metabolic parameter	OR	95% CI	AOR	95% CI
rs2231142	Obesity				
G/G	Non-obesity	1.00			
G/G	Obesity	3.26	0.64-6.51	1.65	0.19-14.23
G/T-T/T	Non-obesity	5.61	1.00-11.49	4.49	1.42-7.64
G/T-T/T	Obesity	13.82	2.41-17.36	12.96	1.34-15.14
rs2231142	Hyperglycemia				
G/G	Non- Hyperglycemia	1.00			
G/G	Hyperglycemia	10.60	1.11-15.75	8.83	0.89-8.92
G/T-T/T	Non-hyperglycemia	7.18	0.84-10.77	9.40	1.72-12.77
G/T-T/T	Hyperglycemia	9.76	4.44-15.51	10.51	3.95-16.65
rs2231142	Triglycerides (TG)				
G/G	Normal TG	1.00			
G/G	High TG	3.15	0.61-16.28	1.38	0.11-17.10
G/T-T/T	Normal TG	5.39	1.02-8.60	11.36	0.85-15.18
G/T-T/T	High TG	11.27	2.15-15.96	7.10	0.58-8.09
rs2231142	High-density lipoprotein cholesterol (HDL-C)				
G/G	Normal HDL-C	1.00			
G/G	Low HDL-C	0.67	0.64-11.50	0.87	0.65-11.49
G/T-T/T	Normal HDL-C	3.62	0.24-5.18	3.63	0.24-5.18
G/T-T/T	Low HDL-C	3.03	0.23-4.56	3.02	0.22-4.56
rs2231142	Blood Pressure (BP)				
G/G	Normal BP	1.00			
G/G	High BP	6.80	0.35-9.12	5.71	0.64-8.92
G/T-T/T	Normal BP	3.31	0.43-8.78	4.34	0.56-9.38
G/T-T/T	High BP	1.70	0.35-10.21	2.61	0.78-8.42

CI=confidence interval, OR=odds ratio, AOR=adjusted odds ratio using a multiple conditional logistic regression model

Discussion

Gout is caused by multiple genetic and environmental factors[4]. The *ABCG2* gene is a high-capacity urate transporter that excretes uric acid from the tubules leading to lowered renal clearance of urate[20,29]. Previous studies have demonstrated that many genetic variations in the *ABCG2* gene are involved in the pathogenesis of gout[19,21,30], especially the *ABCG2* rs2231142 TG-TT genotypes, which have been significantly related to gout in various populations, including the Chinese Han population[31], the genetics of gout in Aotearoa study[32], the population architecture from genomics and epidemiology (PAGE) study[33], and the Framingham and Rotterdam cohort[20]. In this present study, we confirmed that the *ABCG2* rs2231142 TG-TT genotypes are associated with a high risk of gout in a study of Thai men. This is consistent with a European study[34] which found that men with the *ABCG2* rs2231142 T allele had a higher frequency of gout than those with the GG allele. Additionally, our study found that hyperglycemia was also associated with gout due to the SUA levels having a positive effect on blood glucose[35]. One study suggested that high uric acid levels could impair the insulin signaling pathway[36]. One study reported that higher uric acid levels were associated with diabetes mellitus, obesity, metabolic syndrome, and nonalcoholic fatty liver disease[37]. Hyperuricemia can lead not only to gout but has also been associated with metabolic syndrome components[38]. However, our recent study (Table 3) has suggested that high BMI, TG, HDL-C, and BP were not associated with an increased risk of gout, but contrary findings have been demonstrated in other studies. High

BMI[10,11], TG[11], and High BP[10] were associated with the risk of incident gout. lipid profile, including TG and HDL-C, were independently associated with hyperuricemia[15-18].

Our study is the first to find substantial combinations between genotypes and metabolic parameter factors affecting gout in Thai men. The results indicated that the combinations of rs2231142 TG-TT genotypes and the metabolic parameters of obesity and hyperglycemia increased the risk of gout in these men. This risk probably results from the biochemical combinations of the *ABCG2* rs2231142 variant with serum glucose, which causes hyperglycemia and obesity; obesity increases various cytokines, including proinflammatory molecules, tumor necrosis factor-α, and interleukin-6[39-40], and purine metabolism, which causes hyperuricemia leading to gout[36,40]. This may reflect a positive correlation between BMI or FPG status with the rs2231142 TG-TT genotypes and its chronic complications found through pathogenesis studies. This is a combined effect of genetic and metabolic factors on gout risk.

Some limitations of the study must be noted. Firstly, our results are based on a small number of men aged 18-60 years with gout. Further large independent studies are needed to validate our findings. Also, women should be included to observe the sex difference effect. Secondly, only the rs2231142 variant of *ABCG2* was studied, and gene-gene interactions with other genes should be examined in future studies. Other environmental factors may also play an important role in gout risk. Therefore, other environmental factors such as alcohol use, tobacco use, and dietary intake, should be included in the analysis of gene-environment interactions.

Conclusion

In summary, our study confirms that the rs2231142 variant is a likely potential genetic factor in susceptibility to gout occurrence. Our study also found that obesity and hyperglycemia combined with the rs2231142 TG-TT genotypes were associated with the presence of gout in Thai men. Understanding the effect of these combinations may enable better treatment and prognosis of gout patients. Therefore, body weight control and reduction in BMI and fasting plasma glucose levels are recommended in high-risk patients with the *ABCG2* rs2231142 variant.

Acknowledgement

The authors are grateful to the Department of Biochemistry, Faculty of Medicine, Srinakharinwirot University, for their assistance with data collection and data analysis. The authors would like to thank Dr. Ingfar Soontarawirat for her advice on data analysis. Finally, the authors would also like to thank the staff and subjects who were involved in the GUHGTH study.

Conflict of interest

All the authors declare no conflicts of interest.

References

1. Roddy E, Choi HK. Epidemiology of gout. Rheum Dis Clin North Am 2014;40:155-75.
2. Grassi W, De Angelis R. Clinical features of gout. Reumatismo 2012;63:238-45.
3. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. J Rheumatol 2004;31:1582-7.
4. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11:649-62.
5. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, et al. Prevalence of hyperuricemia and gout in Mainland China from 2000 to 2014: a systematic review and meta-analysis. Biomed Res Int 2015;2015:762820.
6. Ragab G, Elshahaly M, Bardin T. Gout: an old disease in a new perspective - a review. J Adv Res 2017;8:495-511.
7. Akizuki S. A population study of hyperuricemia and gout in Japan--analysis of sex, age and occupational differences

in thirty-four thousand people living in Nagano Prefecture. Ryumachi 1982;22:201-8.
8. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350:1093-103.
9. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 2008;336:309-12.
10. Bhole V, de Vera M, Rahman MM, Krishnan E, Choi H. Epidemiology of gout in women: fifty-two-year follow-up of a prospective cohort. Arthritis Rheum 2010;62:1069-76.
11. Cea Soriano L, Rothenbacher D, Choi HK, García Rodríguez LA. Contemporary epidemiology of gout in the UK general population. Arthritis Res Ther 2011;13:R39.
12. Rothenbacher D, Primatesta P, Ferreira A, Cea-Soriano L, Rodríguez LA. Frequency and risk factors of gout flares in a large population-based cohort of incident gout. Rheumatology (Oxford) 2011;50:973-81.
13. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991;266:3008-11.
14. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, et al. Effect of insulin on renal sodium and uric acid handling in essential hypertension. Am J Hypertens 1996;9:746-52.
15. Lippi G, Montagnana M, Luca Salvagno G, Targher G, Cesare Guidi G. Epidemiological association between uric acid concentration in plasma, lipoprotein(a), and the traditional lipid profile. Clin Cardiol 2010;33:E76-80.
16. Sarmah D, Sharma B. A correlative study of uric acid with lipid profile. Asian J Med Sci 2013;4:8-14.
17. Peng TC, Wang CC, Kao TW, Chan JY, Yang YH, Chang YW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015;2015:127596.
18. Ali N, Rahman S, Islam S, Haque T, Molla NH, Sumon AH, et al. The relationship between serum uric acid and lipid profile in Bangladeshi adults. BMC Cardiovasc Disord 2019;19:42.
19. Hurba O, Mancikova A, Krylov V, Pavlikova M, Pavelka K, Stibůrková B. Complex analysis of urate transporters SLC2A9, SLC22A12 and functional characterization of non-synonymous allelic variants of GLUT9 in the Czech population: no evidence of an effect on hyperuricemia and gout. PLoS One 2014;9:e107902.
20. Dehghan A, Köttgen A, Yang Q, Hwang SJ, Kao WL, Rivadeneira F, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. Lancet 2008;372:1953-61.
21. Yang B, Mo Z, Wu C, Yang H, Yang X, He Y, et al. A genome-wide association study identifies common variants influencing serum uric acid concentrations in a Chinese population. BMC Med Genomics 2014;7:10.
22. Yamagishi K, Tanigawa T, Kitamura A, Köttgen A, Folsom AR, Iso H. The rs2231142 variant of the ABCG2 gene is associated with uric acid levels and gout among Japanese people. Rheumatology (Oxford) 2010;49:1461-5.
23. Jiri M, Zhang L, Lan B, He N, Feng T, Liu K, et al. Genetic variation in the ABCG2 gene is associated with gout risk in the Chinese Han population. Clin Rheumatol 2016;35:159-63.
24. Hamajima N, Okada R, Kawai S, Hishida A, Morita E, Yin G, et al. Significant association of serum uric acid levels with SLC2A9 rs11722228 among a Japanese population. Mol Genet Metab 2011;103:378-82.
25. Chen CJ, Tseng CC, Yen JH, Chang JG, Chou WC, Chu HW, et al. ABCG2 contributes to the development of gout and hyperuricemia in a genome-wide association study. Sci Rep 2018;8:3137.
26. Köttgen A, Albrecht E, Teumer A, Vitart V, Krumsiek J, Hundertmark C, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet 2013;45:145-54.
27. Okada Y, Sim X, Go MJ, Wu JY, Gu D, Takeuchi F, et al. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet 2012;44:904-9.
28. Lawrence JS. The epidemiology of chronic rheumatism. Ann Rheum Dis 1964;23:81-2.
29. Woodward OM, Köttgen A, Coresh J, Boerwinkle E, Guggino WB, Köttgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. Proc Natl Acad Sci U S A 2009;106:10338-42.
30. Li R, Miao L, Qin L, Xiang Y, Zhang X, Peng H, et al. A meta-analysis of the associations between the Q141K and Q126X ABCG2 gene variants and gout risk. Int J Clin Exp Pathol 2015;8:9812-23.
31. Wan W, Xu X, Zhao DB, Pang YF, Wang YX. Polymorphisms of uric transporter proteins in the pathogenesis of gout in a Chinese Han population. Genet Mol Res 2015;14:2546-50.

32. Zaidi F, Narang RK, Phipps-Green A, Gamble GG, Tausche AK, So A, et al. Systematic genetic analysis of early-onset gout: ABCG2 is the only associated locus. Rheumatology (Oxford) 2020;59:2544-9.
33. Zhang L, Spencer KL, Voruganti VS, Jorgensen NW, Fornage M, Best LG, et al. Association of functional polymorphism rs2231142 (Q141K) in the ABCG2 gene with serum uric acid and gout in 4 US populations: the PAGE Study. Am J Epidemiol 2013;177:923-32.
34. Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet 2009;5:e1000504.
35. Wardhana W, Rudijanto A. Effect of uric acid on blood glucose levels. Acta Med Indones 2018;50:253-6.
36. Zhu Y, Hu Y, Huang T, Zhang Y, Li Z, Luo C, et al. High uric acid directly inhibits insulin signaling and induces insulin resistance. Biochem Biophys Res Commun 2014;447:707-14.
37. Xiong Q, Liu J, Xu Y. Effects of uric acid on diabetes mellitus and its chronic complications. Int J Endocrinol 2019;2019:9691345.
38. Salehidoost R, Aminorroaya A, Zare M, Amini M. Is uric acid an indicator of metabolic syndrome in the first-degree relatives of patients with type 2 diabetes? J Res Med Sci 2012;17:1005-10.
39. Sell H, Eckel J. Adipose tissue inflammation: novel insight into the role of macrophages and lymphocytes. Curr Opin Clin Nutr Metab Care 2010;13:366-70.
40. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796-808.