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Review Article

Interrelationship of Uric Acid, Gout, and Metabolic Syndrome: Focus on Hypertension, Cardiovascular Disease, and Insulin Resistance

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The mean serum uric acid level and the prevalence of hyperuricemia have increased over the past few decades. Hyperuricemia is considered to be responsible for the increased risk of hypertension, insulin resistance, and cardiovascular disease. Metabolic syndrome also contributes to the development of type II diabetes mellitus and cardiovascular disease. Despite the close relationships between uric acid and the components of metabolic syndrome, the causal effect of uric acid on these clinical issues is unclear. Recent studies have revealed the possible development of metabolic syndrome mediated by fructose-induced hyperuricemia. This review summarizes the available clinical and experimental data supporting the causal effect of uric acid on the components of metabolic syndrome, including hypertension, cardiovascular disease, and insulin resistance. **(J Rheum Dis 2018;25:19-27)**

Key Words. Uric acid, Hyperuricemia, Gout, Metabolic syndrome

INTRODUCTION

Uric acid is a ubiquitous byproduct of purine metabolism in humans and higher primates [1]. Precipitation of uric acid (monosodium urate [MSU] crystals) in joints and soft tissues results in the development of gout. Hyperuricemia is defined as a serum urate level above 6.8 mg/mL, which is the limit of urate solubility at physiologic temperature and pH; thus, concentrations greater than this promote the deposition of MSU crystals. However, uric acid also has antioxidant properties in the extracellular environment including biologic fluids [2]. Therefore, increased uric acid level is believed to play a beneficial role in the condition of oxidative stress. In contrast, hyperuricemia can show oxidant effects by forming radicals in reaction with other oxidant molecules. Furthermore, uptake of uric acid by vascular smooth muscle cells and adipocytes led to increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases [3]. Based on these observations, it has been proposed that uric acid or hyperuricemia is related to risk of hypertension, renal diseases, cardiovascular disease, and type 2 diabetes mellitus in various clinical and epidemiological studies [4,5].

Metabolic syndrome is a group of physiological and metabolic abnormalities including obesity, abnormal glucose metabolism, dyslipidemia, and hypertension [6]. Metabolic syndrome is known to be related with increased risk of cardiovascular disease, hypertension, and type II diabetes mellitus [7,8]. There is growing evidence that there is close association between uric acid and metabolic syndrome [9-11]. In addition, the prevalence of metabolic syndrome in patients with gout is higher than in control groups [12,13]. Here, this paper reviews the complex interrelationship between hyperuricemia/gout and metabolic syndrome as well as its components including hy-

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pertension, cardiovascular disease, and insulin resistance.

MAIN SUBJECTS

Uric acid and metabolic syndrome

In 1998, the World Health Organization (WHO) first described 'metabolic syndrome' [14]. Classification criteria for metabolic syndrome have been proposed by the WHO, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [15], and the International Diabetes Federation (Table 1) [16]. However, the definition of metabolic syndrome is still not consistent. Nevertheless, many studies about the effect of elevated uric acid on the development of metabolic syndrome have been performed in the last several decades. Large epidemiologic studies regarding the association between hyperuricemia and metabolic syndrome have shown that increased serum urate concentration is often observed in subjects with metabolic syndrome [9-11]. Choi and Ford [9] assessed data from 8,669 participants in The Third National Health and Nutrition Examination Survey (NHANES-III) (1988～1994) and demonstrated that the prevalence of metabolic syndrome increased with increasing serum uric acid levels. In another study, among a total of 2,374 subjects who received a health examination, subjects with hyperuricemia had a 1.63-fold increased risk of metabolic syndrome compared with those without hyperuricemia on the basis of criteria of metabolic syndrome defined by the American Heart Association/National Heart, Lung, and Blood Institute [17]. In two other studies, mean serum uric acid level in patients with metabolic syndrome was about 0.5～1.0 mg/dL higher than controls [18,19]. In addition, another study showed that serum uric acid level increased with number of components of metabolic syndrome after adjusting for age, sex, creatinine clearance, and alcohol/diuretic use [19]. Recently, hyperuricemia is recognized as a distinct feature and/or major associated factor of metabolic syndrome (Figure 1).

Gout and metabolic syndrome

The prevalence of metabolic syndrome and hyperuricemia/gout has steadily increased. There are data for the prevalence of gout and hyperuricemia in US adults from the NHANES-III (1988～1994) and NHANES 2007～2008, and they show that the prevalence of these conditions is substantial and has increased over the past two decades [20]. In addition, the prevalence of metabolic syndrome persistently increased in data from the NHANES-III to the NHANES 1999～2006 in the US population [21]. Similarly, in the Korean population over 20 years old, Lim et al. [22] demonstrated that the prevalence of metabolic syndrome gradually increased from 24.9% in 1998 to 31.3% in 2007. Several clinical investigations showed a higher prevalence of metabolic syndrome in patients with gout compared to the general population [12,13,23]. The prevalence of metabolic syndrome in Korean patients with gouty arthritis was 30%～

Table 1. Definitions of the metabolic syndrome: comparison of WHO, NCEP ATP III, and IDF classification criteria

Risk factors	WHO [14]	NCEP ATP III [15]	IDF [16]
Criteria	DM/IFG or IGT or IR plus at least two of the following	Any ≥3 of the following 5 criteria	Increased WC (ethnicity specific) plus at least two of the following
Obesity	Waist-to-hip ratio >0.90 in men and >0.85 in women and/or BMI >30 kg/m^2	WC ≥102 cm in men or ≥88 cm in women	WC criteria dependent on ethnicity
Triglycerides	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL
HDL cholesterol	<35 mg/dL in men and <39 mg/dL in women	<40 mg/dL in men and <50 mg/dL in women	<40 mg/dL in men and <50 mg/dL in women
Hypertension	≥140/90 mmHg	≥130 mmHg systolic or ≥85 mmHg diastolic	≥130 mmHg systolic or ≥85 mmHg diastolic
Hyperglycemia	IGT, IFG, or type 2 DM	≥100 mg/dL	≥100 mg/dL
Microalbuminuria	>30 mg albumin/g creatinine		

WHO: World Health Organization, NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III, IDF: International Diabetes Federation, HDL: highdensity lipoprotein, DM: diabetes mellitus, IFG: impaired fasting glucose (fasting plasma glucose level, 100～125 mg/dL), IGT: impaired glucose tolerance (2 h plasma glucose level after 75 g glucose load, 140～199 mg/dL), IR: insulin resistance, WC: waist circumference, BMI: body mass index.

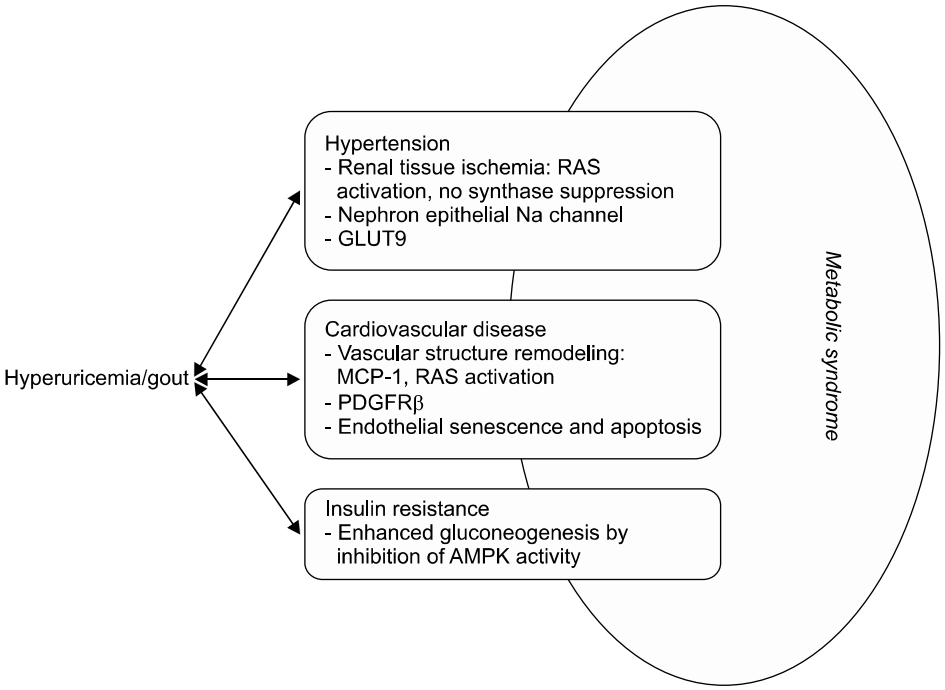

Figure 1. Uric acid contributes to different component features of metabolic syndrome. RAS: renin-angiotensin system, NO: nitric oxide, GLUT9: glucose transporter 9, MCP-1: monocyte chemoattractant protein-1, PDGFR β: platelet-derived growth factor receptor beta, AMPK: adenosine monophosphate kinase.

42% according to NCEP ATP III guidelines and 50%～59% according to the WHO Asia-Pacific obesity criteria, both of which were significantly higher than the normal control groups [13,23]. These findings showed parallel increasing prevalence of both metabolic syndrome and gout and suggested that the two diseases are linked.

Hyperuricemia and hypertension

Epidemiologic studies demonstrated that hyperuricemia is strongly associated with greater risk for hypertension [24,25]. However, the association between uric acid and incidence of hypertension are still controversial. A recent meta-analysis of 25 studies with a total of 97,824 participants, concluded that hyperuricemia can augment the risk of systemic hypertension, with a dose-dependent relationship [26]. Furthermore, a cohort study in Israel assessed whether normal serum uric acid level, below 5～6 mg/dL, might be related to hypertension and found that a higher serum uric acid concentration, even within the normal range, increased the risk of hypertension [27].

Even though there is a striking relationship between uric acid and hypertension, there is a lack of evidence explaining the mechanism by which uric acid leads to the development of hypertension. Mazzali et al. [28] developed a rat experimental model with mild hyperuricemia by feeding oxonic acid, a uricase inhibitor. In this experiment, elevated blood pressure was found in hyperuricemic rats after three weeks, whereas control rats had normal blood pressure. An in vivo study showed that hypertension in experimental rats was found to be associated with uric acid, which leads to an ischemic type of injury with collagen deposition, macrophage infiltration, activation of the renin-angiotensin system, and suppression of nitric oxide (NO) synthase. In addition, it was also found that hyperuricemia directly induced renal arteriopathy through proliferation of vascular smooth muscle cells, leading to hypertension in rat [29]. The distal nephron epithelial sodium channel (ENaC) is a key regulator of sodium balance and blood pressure. In a recent in vivo experiment, uric acid increased the expression of three ENaC subunits in murine cortical colleting ducts in hyperuricemic rats with a consequent decrease in urinary sodium excretion, ultimately causing hypertension [30]. Glucose transporter (GLUT)-9, expressed in both apical and basolateral membranes of the distal nephron, is a urate transporter that controls urate homeostasis and determines serum uric acid level. In a family-based study, the risk allele (T) of the rs734555 polymorphism of the GLUT9 gene was strongly associated with serum uric acid level, and subjects with the TT genotype showed higher systolic blood pressure than other genotypes [31]. These findings might provide evidence for enhanced understanding mechanism of uric acid-induced hypertension.

Considering the close association between hyperuricemia and hypertension, serum uric acid might be a potent ther-

apeutic target to control blood pressure. In an in vivo rat model, hypertension developed in hyperuricemic rats and was effectively prevented by concurrent treatment with uric acid-lowering agents including allopurinol and benziodarone [28]. In a randomized, double-blind, placebo-controlled, crossover human trial involving 30 adolescents who had newly diagnosed essential hypertension and serum uric acid level ≥6 mg/dL, systolic blood pressure in patients treated with allopurinol (400 mg/day) was significantly decreased, whereas the placebo group experienced no change in blood pressure [32]. Using data from the UK Clinical Practice Research Datalink, allopurinol use was independently associated with a fall in both systolic and diastolic blood pressure after allopurinol initiation [33]. In contrast, a lowering effect of xanthine oxidase inhibitors (allopurinol and febuxostat) on blood pressure was not found in adult hypertensive patients with hyperuricemia [34]. Therefore, a consistent effect of urate-lowering therapy on hyperuricemic hypertension remains to be determined.

Hyperuricemia and cardiovascular disease

Galen, a Roman physician of the 2nd century, described the association between gout, a disease caused by 'debauchery and intemperance,' and cardiovascular diseases [35]. For several decades, many studies investigated whether hyperuricemia or gout was a critical determinant for increased risk of cardiovascular diseases. Recently, these studies have not only supported this relationship, but also demonstrated that uric acid is an independent risk factor for the development of cardiovascular diseases [35]. In an analysis of the Framingham Cohort Study data set, patients with gout experienced 60 more frequent coronary heart disease and a two-fold greater incidence of angina pectoris compared to those without gout [36]. Logistic regression analysis of data from 2,498 participants in the Coronary Artery Risk Development in Young Adults study found that prevalence of coronary calcification increased with serum uric acid level, which implies that hyperuricemia is an independent risk factor for subclinical coronary artery disease in young adults [37]. Stack et al. [38] reported that the hazard ratio (HR) for subjects with gout from data of the NHANES-III (1988-1994) was 1.58 (95% confidence interval [CI], 1.13～2.19) for cardiovascular mortality, and adjusted HR per 1 mg/dL increase in uric acid was 1.16 (95% CI, 1.10～1.22) for total and cardiovascular mortality. In addition, they found that 9.7% of subjects with gout had congestive heart failure at baseline compared with 1.8% of those without gout.

There is a question as to whether urate-lowering therapy can reduce the risk of cardiovascular disease. Predictors for development and/or progression of atherosclerosis or endothelial cell function include brachial artery flow-mediated dilatation (FMD), carotid intima-media thickness (IMT), and aortic stiffness index (AoSI). Increased serum uric acid level is a potent risk factor for subclinical atherosclerosis and endothelial dysfunction, showing impaired FMD, increased IMT, and increased AoSI [39,40]. Considering the effect of urate-lowering drugs on atherosclerosis, allopurinol for three years in diabetic patients with hyperuricemia reduced carotid IMT [41]. The therapeutic effect of urate-lowering therapy, specifically a uricouric agent (benzbromarone), on congestive heart failure was not observed [42], whereas xanthine oxidase inhibitors alleviated systolic overload-induced left ventricular hypertrophy and dysfunction in a mouse model [43]. However, allopurinol failed to improve clinical status, exercise capacity, quality of life, or left ventricular ejection fraction at 24 weeks in the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients Study, which was designed to identify the effect of a xanthine oxidase inhibitor on outcomes in patients with heart failure and hyperuricemia [44]. Based on these findings, whether urate-lowering treatment could lead to beneficial outcomes of cardiovascular diseases remains a matter of debate.

It is well known that uric acid directly or indirectly induces remodeling of vascular structures. However, the precise mechanism of uric acid-induced cardiovascular disease has not been clearly defined. It has been suggested that uric acid induces proliferation of vascular smooth muscle cells and/or regulates various signal pathways. Vascular changes by uric acid were mediated by enhanced expression of monocyte chemoattractant protein-1 (MCP-1) and activation of the renin-angiotensin system [29,45]. In a recent in vitro study, uric acid stimulated a 2.2-fold increase of platelet-derived growth factor receptor beta (PDGFR β) phosphorylation in primary cultured vascular smooth muscle cells from rat aorta, in addition to p38 mitogen-activated protein kinase and p44/42 [46]. Uric acid-induced oxidative stress, which increases intracellular free oxygen species, led to the development of endothelial senescence and apoptosis using human umbilical vein endothelial cells; this effect was reversed by antioxidants including N-acetylcysteine and

tempol [47]. This observation implies that uric acid-induced oxidative stress involves endothelial dysfunction, which could be novel therapeutic target for cardiovascular disease.

Hyperuricemia and insulin resistance

Insulin is the most important biological hormone that regulates energy metabolism, including carbohydrates, lipid, and protein. Insulin promotes the absorption of glucose from the blood into liver and skeletal muscle cells [48]. Insulin resistance is defined as a metabolic state in which insulin sensitivity is abnormally low at physiological insulin concentrations, eventually leading to hyperinsulinemia. Insulin resistance has been thought to be a strong determinant for the development of some components of metabolic syndrome including dyslipidemia, diabetes mellitus, and hypertension.

Despite intensive studies, a causative relationship between uric acid and insulin resistance has not been clarified. It is relatively well established that there is a higher incidence of metabolic syndrome and insulin resistance in patients with gout compared with those of the general population [49]. In an earlier clinical study, decreased urinary uric acid clearance was noted to be inversely proportional to increased insulin resistance, finally inducing an increase in serum uric acid level [50]. Euglycemic hyperinsulinemia by exogenous insulin infusion has been shown to decrease urinary excretion of uric acid, sodium, and potassium in both normal and hypertensive subjects [51,52]. In addition, Doshi et al. [53] discovered that the urate reabsorption transporter URAT1 protein was involved in obesity/metabolic syndrome-associated hyperuricemia using two obesity mouse models. Based on these available data, insulin resistance can be attributed to the disturbance of urate regulation such as hyperuricemia.

In contrast, in an analysis of nondiabetic participants from the Atherosclerosis Risk in Communities Study (n=9,020) followed from 1987 to 1998, hyperuricemia was associated with an increase in the risk of future development of hyperinsulinemia [54]. Similarly, the multiple risk factor intervention trial to determine the relationship between gout and risk of incident type II diabetes mellitus suggested that men with gout are at a higher future risk of diabetes mellitus [55]. A uric acid-lowering effect by the xanthine oxidase inhibitor allopurinol improved low grade inflammation (i.e., macrophage infiltration) and reduced insulin resistance in an obese murine model with metabolic syndrome [56].

It is known that increased hepatic gluconeogenesis is a distinct feature of insulin resistance and diabetes mellitus. Some hypotheses for uric acid-induced gluconeogenesis metabolism have been suggested. For example, Cicerchi et al. [57] demonstrated that uric acid led to enhanced hepatic gluconeogenesis by inhibition of adenosine monophosphate kinase, which regulates rate-limiting enzymes cytoplasmic phosphoenolpyruvate carboxykinase and glucose-6-phosphatase involved in gluconeogenesis in liver. This finding suggests that urate-lowering therapy might reduce gluconeogenesis in the clinical condition of gout with metabolic syndrome.

Fructose and metabolic syndrome

Fructose is a monosaccharide naturally present in fruits, vegetables, and honey and is mainly absorbed into systemic circulation in the small intestine via specific transporters such as GLUT-2 and GLUT-5 and then metabolized largely in the liver to produce glucose, lactate, triglycerides, and uric acid [58,59]. Fructose is frequently used to sweeten processed food and beverages. High-fructose corn syrup (HFCS) is one of the most widely used food ingredients and is used in many soft drinks, dairy products, and canned jams. It has been well recognized that a diet high in fructose is tightly associated with insulin resistance, chronic inflammation, and other metabolic diseases including metabolic syndrome; it also disturbs function of various organs and tissues in the body [60,61].

Since HFCS was first introduced in 1967, the consumption of fructose has increased considerably [62]. The marked increase in soft drink and fructose-containing processed products is parallel with the increase in serum uric acid [63,64]. Similarly, our study confirmed that higher consumption of sugar-sweetened soft drinks increased the risk of hyperuricemia in males (adjusted odds ratio [OR], 1.35; 95% CI, 1.07~1.71) and in females (adjusted OR, 1.40; 95% CI, 1.03~1.90) [65].

In regard to the mechanism of fructose-induced production of uric acid, fructose is known to increase uric acid production though increasing adenosine triphosphate degradation to adenosine monophosphate (AMP), a uric acid precursor [1,66]. As a net result, increased intracellular AMP leads to generation of hypoxanthine and xanthine through activation of catabolic pathways, finally inducing uric acid formation. Based on these observations, some epidemiologic studies supported that fructose intake might increase the risk of development of

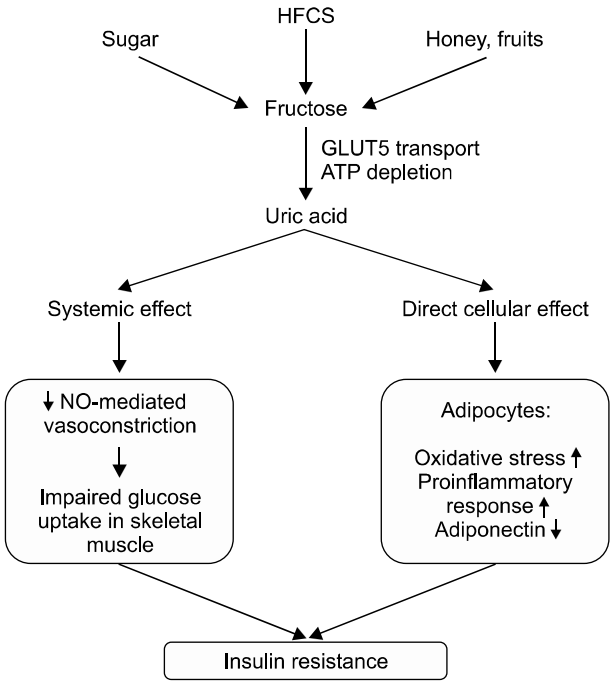

Figure 2. Mechanisms of insulin resistance by fructose and uric acid. HFCS: high-fructose corn syrup, GLUT5: glucose transporter 5, ATP: adenosine triphosphate, NO: nitric oxide.

gout [67,68].

Earlier studies recognized that a diet high in sucrose could induce features of metabolic syndrome such as hyperglycemia, insulin resistance, and hypertension [69,70]. Fructose was found to be responsible for these metabolic disturbances [71]. Moreover, there is evidence that fructose-induced hyperuricemia leads to insulin resistance [72,73]. Urate-lowering therapy using xanthine oxidase inhibitors such as allopurinol and febuxostat in fructose-feeding rats can prevent the development of hyperinsulinemia, hypertriglyceridemia, and systolic hypertension in the metabolic syndrome. Two hypotheses have been raised that account for fructose-induced insulin resistance (Figure 2). First, uric acid inhibits insulin-mediated endothelial NO release, leads to decreased blood flow to skeletal muscle, and subsequently blocks glucose uptake into skeletal muscle [74]. The second mechanism is mediated by increased oxidative stress and an inflammatory response in adipocytes by uric acid [75,76]. Moving forward, further research should identify whether fructose itself or fructose-mediated uric acid is associated with the pathogenic mechanism of metabolic syndrome.

CONCLUSION

The prevalence of hyperuricemia and gout has been gradually increasing over the past several decades. Metabolic syndrome is defined as a cluster of metabolic and physiologic abnormalities such as hypertension, obesity, dyslipidemia, and abnormal glucose metabolism. The observation that increased serum urate concentration is often observed in subjects with metabolic syndrome is present in a number of epidemiologic studies. As shown in Figure 1, uric acid or hyperuricemia contribute the development of metabolic syndrome through diverse mechanisms. Urate-lowering therapy might be beneficial to prevent or reduce the development of metabolic syndrome itself or its components. Despite the effect of uric acid on metabolic syndrome, a causal relationship between hyperuricemia/gout and metabolic syndrome has not been clearly determined.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Choi HK, Mount DB, Reginato AM; American College of Physicians; American Physiological Society. Pathogenesis of gout. Ann Intern Med 2005;143:499-516.
2. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A 1981;78:6858-62.
3. 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:C584-96.
4. Kim KY, Ralph Schumacher H, Hunsche E, Wertheimer AI, Kong SX. A literature review of the epidemiology and treatment of acute gout. Clin Ther 2003;25:1593-617.
5. 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.
6. Sarafidis PA, Nilsson PM. The metabolic syndrome: a glance at its history. J Hypertens 2006;24:621-6.
7. Liberopoulos EN, Mikhailidis DP, Elisaf MS. Diagnosis and management of the metabolic syndrome in obesity. Obes Rev 2005;6:283-96.
8. Daskalopoulou SS, Mikhailidis DP, Elisaf M. Prevention and treatment of the metabolic syndrome. Angiology 2004;55:589-612.
9. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med 2007;120:442-7.

10. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic syndrome in women and men. Metabolism 2008;57:845-52.
11. Ryu S, Song J, Choi BY, Lee SJ, 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: 245-52.
12. Jung JH, Song GG, Ji JD, Lee YH, Kim JH, Seo YH, et al. Metabolic syndrome: prevalence and risk factors in Korean gout patients. Korean J Intern Med 2016 Oct 12 [Epub]. DOI: 10.3904/kjim.2016.062.
13. Yoo HG, Lee SI, Chae HJ, Park SJ, Lee YC, Yoo WH. Prevalence of insulin resistance and metabolic syndrome in patients with gouty arthritis. Rheumatol Int 2011;31: 485-91.
14. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
16. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet 2005;366:1059-62.
17. Chen LY, Zhu WH, Chen ZW, Dai HL, Ren JJ, Chen JH, et al. Relationship between hyperuricemia and metabolic syndrome. J Zhejiang Univ Sci B 2007;8:593-8.
18. López-Suárez A, Elvira-González J, Bascuñana-Quirell A, Rosal-Obrador J, Michán-Doña A, Escribano-Serrano J, et al. Serum urate levels and urinary uric acid excretion in subjects with metabolic syndrome. Med Clin (Barc) 2006;126: 321-4.
19. Hjortnaes J, Algra A, Olijhoek J, Huisman M, Jacobs J, van der Graaf Y, et al. Serum uric acid levels and risk for vascular diseases in patients with metabolic syndrome. J Rheumatol 2007;34:1882-7.
20. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63:3136-41.
21. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. Diabetes Care 2011;34:216-9.
22. Lim S, Shin H, Song JH, Kwak SH, Kang SM, Won Yoon J, et al. Increasing prevalence of metabolic syndrome in Korea: the Korean National Health and Nutrition Examination Survey for 1998-2007. Diabetes Care 2011;34:1323-8.
23. Rho YH, Choi SJ, Lee YH, Ji JD, Choi KM, Baik SH, et al. Prevalence of the metabolic syndrome in patients with gout. J Korean Rheum Assoc 2004;11:349-57.
24. Sun HL, Pei D, Lue KH, Chen YL. Uric acid levels can predict metabolic syndrome and hypertension in adolescents: a 10-year longitudinal study. PLoS One 2015;10:e0143786.
25. Yokoi Y, Kondo T, Okumura N, Shimokata K, Osugi S, Maeda K, et al. Serum uric acid as a predictor of future hypertension: Stratified analysis based on body mass index and age. Prev Med 2016;90:201-6.
26. Wang J, Qin T, Chen J, Li Y, Wang L, Huang H, et al. Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. PLoS One 2014;9:e114259.
27. Leiba A, Vinker S, Dinour D, Holtzman EJ, Shani M. Uric acid levels within the normal range predict increased risk of hypertension: a cohort study. J Am Soc Hypertens 2015;9: 600-9.
28. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38:1101-6.
29. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991-7.
30. Xu W, Huang Y, Li L, Sun Z, Shen Y, Xing J, et al. Hyperuricemia induces hypertension through activation of renal epithelial sodium channel (ENaC). Metabolism 2016;65:73-83.
31. Mallamaci F, Testa A, Leonardis D, Tripepi R, Pisano A, Spoto B, et al. A polymorphism in the major gene regulating serum uric acid associates with clinic SBP and the white-coat effect in a family-based study. J Hypertens 2014;32:1621-8.
32. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008;300: 924-32.
33. Beattie CJ, Fulton RL, Higgins P, Padmanabhan S, McCallum L, Walters MR, et al. Allopurinol initiation and change in blood pressure in older adults with hypertension. Hypertension 2014;64:1102-7.
34. Kohagura K, Tana T, Higa A, Yamazato M, Ishida A, Nagahama K, et al. Effects of xanthine oxidase inhibitors on renal function and blood pressure in hypertensive patients with hyperuricemia. Hypertens Res 2016;39:593-7.
35. Bhole V, Krishnan E. Gout and the heart. Rheum Dis Clin North Am 2014;40:125-43.
36. Abbott RD, Brand FN, Kannel WB, Castelli WP. Gout and coronary heart disease: the Framingham study. J Clin Epidemiol 1988;41:237-42.
37. Krishnan E, Pandya BJ, Chung L, Dabbous O. Hyperuricemia and the risk for subclinical coronary atherosclerosis--data from a prospective observational cohort study. Arthritis Res Ther 2011;13:R66.
38. Stack AG, Hanley A, Casserly LF, Cronin CJ, Abdalla AA, Kiernan TJ, et al. Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. QJM 2013;106:647-58.
39. Erdogan D, Gullu H, Caliskan M, Yildirim E, Bilgi M, Ulus T, et al. Relationship of serum uric acid to measures of endothelial function and atherosclerosis in healthy adults. Int J Clin Pract 2005;59:1276-82.
40. Kato M, Hisatome I, Tomikura Y, Kotani K, Kinugawa T, Ogino K, et al. Status of endothelial dependent vasodilation in patients with hyperuricemia. Am J Cardiol 2005;96: 1576-8.
41. Liu P, Wang H, Zhang F, Chen Y, Wang D, Wang Y. The effects of allopurinol on the carotid intima-media thickness in patients with type 2 diabetes and asymptomatic hyper-

uricemia: a three-year randomized parallel-controlled study. Intern Med 2015;54:2129-37.
42. Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Osaki S, et al. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. Circ Heart Fail 2010; 3:73-81.
43. Xu X, Hu X, Lu Z, Zhang P, Zhao L, Wessale JL, et al. Xanthine oxidase inhibition with febuxostat attenuates systolic overload-induced left ventricular hypertrophy and dysfunction in mice. J Card Fail 2008;14:746-53.
44. Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, et al. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study. Circulation 2015;131:1763-71.
45. 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;41:1287-93.
46. Kırça M, Oğuz N, Çetin A, Uzuner F, Yeşilkaya A. Uric acid stimulates proliferative pathways in vascular smooth muscle cells through the activation of p38 MAPK, p44/42 MAPK and PDGFRβ. J Recept Signal Transduct Res 2017;37: 167-73.
47. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens 2010;28:1234-42.
48. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
49. Krishnan E. Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. Rheumatology (Oxford) 2010;49:1229-38.
50. 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.
51. 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.
52. Quiñones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, et al. Effect of insulin on uric acid excretion in humans. Am J Physiol 1995;268:E1-5.
53. Doshi M, Takiue Y, Saito H, Hosoyamada M. The increased protein level of URAT1 was observed in obesity/metabolic syndrome model mice. Nucleosides Nucleotides Nucleic Acids 2011;30:1290-4.
54. Carnethon MR, Fortmann SP, Palaniappan L, Duncan BB, Schmidt MI, Chambless LE. Risk factors for progression to incident hyperinsulinemia: the Atherosclerosis Risk in Communities Study, 1987-1998. Am J Epidemiol 2003;158: 1058-67.
55. Choi HK, De Vera MA, Krishnan E. Gout and the risk of type 2 diabetes among men with a high cardiovascular risk profile. Rheumatology (Oxford) 2008;47:1567-70.
56. Baldwin W, McRae S, Marek G, Wymer D, Pannu V, Baylis C, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. Diabetes 2011; 60:1258-69.
57. Cicerchi C, Li N, Kratzer J, Garcia G, Roncal-Jimenez CA, Tanabe K, et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids. FASEB J 2014;28:3339-50.
58. Van den Berghe G. Fructose: metabolism and short-term effects on carbohydrate and purine metabolic pathways. Prog Biochem Pharmacol 1986;21:1-32.
59. Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, et al. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? Endocr Rev 2009;30:96-116.
60. Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. Nat Rev Gastroenterol Hepatol 2010;7:251-64.
61. Bomback AS, Derebail VK, Shoham DA, Anderson CA, Steffen LM, Rosamond WD, et al. Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. Kidney Int 2010;77:609-16.
62. White JS. Straight talk about high-fructose corn syrup: what it is and what it ain't. Am J Clin Nutr 2008;88:1716S-21S.
63. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2005;52:283-9.
64. Choi JW, Ford ES, Gao X, Choi HK. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2008;59:109-16.
65. Bae J, Chun BY, Park PS, Choi BY, Kim MK, Shin MH, et al. Higher consumption of sugar-sweetened soft drinks increases the risk of hyperuricemia in Korean population: The Korean Multi-Rural Communities Cohort Study. Semin Arthritis Rheum 2014;43:654-61.
66. Fox IH, Kelley WN. Studies on the mechanism of fructose-induced hyperuricemia in man. Metabolism 1972; 21:713-21.
67. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 2008;336:309-12.
68. Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. JAMA 2010;304:2270-8.
69. al-Nagdy S, Miller DS, Yudkin J. Changes in body composition and metabolism induced by sucrose in the rat. Nutr Metab 1970;12:193-219.
70. Sleder J, Chen YD, Cully MD, Reaven GM. Hyperinsulinemia in fructose-induced hypertriglyceridemia in the rat. Metabolism 1980;29:303-5.
71. Bruckdorfer KR, Kang SS, Yudkin J. Plasma concentrations of insulin, corticosterone, lipids and sugars in rats fed on meals with glucose and fructose. Proc Nutr Soc 1973;32: 12A-3A.
72. 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:F625-31.
73. Sánchez-Lozada LG, Tapia E, Bautista-García P, Soto V,

Avila-Casado C, Vega-Campos IP, et al. Effects of febuxostat on metabolic and renal alterations in rats with fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2008;294:F710-8.
74. Hsu MC, Wang ME, Jiang YF, Liu HC, Chen YC, Chiu CH. Long-term feeding of high-fat plus high-fructose diet induces isolated impaired glucose tolerance and skeletal muscle insulin resistance in miniature pigs. Diabetol Metab Syndr 2017;9:81.
75. Cheung KJ, Tzameli I, Pissios P, Rovira I, Gavrilova O, Ohtsubo T, et al. Xanthine oxidoreductase is a regulator of adipogenesis and PPARgamma activity. Cell Metab 2007;5:115-28.
76. Marek G, Pannu V, Shanmugham P, Pancione B, Mascia D, Crosson S, et al. Adiponectin resistance and proinflammatory changes in the visceral adipose tissue induced by fructose consumption via ketohexokinase-dependent pathway. Diabetes 2015;64:508-18.