

Received: 2016.05.15
Accepted: 2016.07.11
Published: 2017.02.13

The Role of Uric Acid in Hypertension of Adolescents, Prehypertension and Salt Sensitivity of Blood Pressure

Department of Cardiology, First Affiliated Hospital of Medical School, Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE **Yang Wang***
AE **Jia-Wen Hu***
EF **Yong-Bo Lv**
E **Chao Chu**
E **Ke-Ke Wang**
F **Wen-Ling Zheng**
E **Yu-Meng Cao**
E **Zu-Yi Yuan**
AG **Jian-Jun Mu**

* Equally contributed to this work

Corresponding Authors:

Source of support:





Yang Wang, e-mail: wangyangxk@126.com, Jian-Jun Mu, e-mail: mujjun@163.com

The National Natural Science Foundation of China (No. 81370357 and No. 81570381), the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University, China (No. XJTU1AF-CRF-2015-006), and the National Basic Research Program (also called 973 Program) of China (No. 2012CB517804)

Uric acid is the end product of purine metabolism. Metabolic disorders of uric acid are associated with many disease states. Substantial evidence suggests the possible role of uric acid as a mediator of high blood pressure. Elevated uric acid is closely associated with new onset essential hypertension in adolescents and prehypertension; and urate-lowering agents can significantly improve these early stages of hypertension. Uric acid also influences salt sensitivity of blood pressure through two phases. Local renin-angiotensin-aldosterone system activation initiates renal damage, arteriopathy, and endothelium dysfunction, which is followed by the dysregulation of sodium homeostasis, thereby leading to increased salt sensitivity. In this review we summarize the available evidence to contribute to a better understanding of the casual relationship between uric acid and early or intermediate stages of hypertension. We hope our review can contribute to the prevention of hypertension or provide new insights into a treatment that would slow the progression of hypertension.

MeSH Keywords: **Child • Hypertension • Prehypertension • Uric Acid**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/899563>

 2678  —  —  63



Background

Hypertension is the most common chronic disease in developing and developed countries. It is diagnosed in 20–50% of the adult population, and 10–30% of adults suffer from resistant hypertension. The number of affected patients continues to rise. Known nonpharmacological methods and drugs registered/approved for treatment of arterial hypertension often do not achieve their intended therapeutic targets. Inadequate blood pressure (BP) control leads to life-threatening complications, such as stroke, heart diseases, and chronic kidney disease [1,2]. These dismaying situations and the profound health impact of hypertension necessitate research efforts on early prevention and control of hypertension.

Uric acid (UA) is the end product of purine metabolism; its transformation to allantoin is catalyzed by urate oxidase in most mammals, and it is predominantly cleared by the kidneys [3]. However, mutations in the uricase gene occurred during human evolution, and the levels of serum UA in humans are higher than those in other mammals [4]. Compelling evidence indicates an intimate relationship between serum UA level and hypertension [5]. Elevated UA can contribute to the development of hypertension through vascular dysfunction [6] and can drive the progression of target organ damages [5,7]. In addition, serum UA is associated with hypertension in adolescents, prehypertension, and salt sensitivity of BP, which are the early and intermediate stages of essential hypertension [8–10]. Recognition of these early and intermediate stages of hypertension is helpful to prevent advanced hypertension. In this review, we summarize the relevant studies on the relationship between UA and the early and intermediate stages of hypertension. We also attempt to determine whether UA interventions can help prevent hypertension.

UA and Hypertension in Adolescents

Evidence indicates that the roots of adult hypertension are present in childhood [11]. Elevated BP during childhood is an excellent predictor of hypertension in adults [10]. Moreover, primary hypertension, which is the most common type in adolescents, can exert profound influence on future cardiovascular disease and related organ damage [12].

Adolescents have relatively fewer confounding factors, such as diabetes, cardiovascular diseases, age-related illness, renal dysfunction, and unhealthy lifestyles, than adults. Thus, they are the ideal population to study the early physiological steps that initiate essential hypertension. The majority of studies suggest a close relationship between serum UA and hypertension in the young; this relationship is closer in adolescents than in older people [13,14]. The Moscow Children's

Hypertension Study determined hyperuricemia (>8 mg/dL) in 9.5% of adolescents with normal BP, 49% of age-matched children with borderline hypertension, and 73% with moderate and severe hypertension [15]. These findings are supported by the Hungarian Children's Health Study, which was a longitudinal study conducted for 13 years on 17,624 adolescents [16]. These studies did not exclude hypertensive children, thereby influencing the extrapolation of these results. Thus, the exact role of UA, whether as a prominent causal factor or as a marker accompanied with hypertension, remains confusing.

A cross-sectional study was conducted in 501 children with relatively high cardiovascular risk to elucidate the relationship between serum UA and hypertension in the young. The findings indicated a 1 mg/dL increase in serum UA contributed to at least a 50% increase in the presence of prehypertension or hypertension (OR=1.60, $p<0.01$; OR=1.54, $p<0.01$, respectively). The risk doubled in children who were at the top gender-specific UA quartile (OR=2.25, 95% CI 1.15–4.38, $p=0.01$; OR=2.04, 95% CI 1.12–3.73, $p=0.02$) [17]. The study considered many major confounding factors that were implicated at least in part in the development of hypertension; thus, the results are convincing. In addition, a 10-year longitudinal study of 5,748 adolescents, which followed participants for a median of 7.2 years, also determined that plasma UA levels can predict the occurrence of hypertension regardless of gender [18]. This finding is also supported by results from the Bogalusa Heart Study [13]. Furthermore, it has been reported that normotensive children with hypertensive parents encounter high plasma UA levels [19]. These children also have a high risk of becoming hypertensive during their adolescent years compared with children with normotensive parents [20], thereby strengthening the link between these two factors. The elevation of UA levels tends to be a causal risk factor or a predictor for primary hypertension rather than a result of hypertension; this observation has been confirmed by the phenomenon that an increased UA level can rarely be observed in secondary hypertension [21]. Similar results were also reported in other studies. A study by Bobridge et al. showed that after adjusting for multiple confounders, serum UA was independently associated with BP both in boys and girls [22]. However, all these studies used casual BP levels in their analysis, thereby increasing bias. Ambulatory BP monitoring has been demonstrated to be superior over casual clinic measurement in the assessment of BP. The work of Jones et al. showed that serum UA was associated with 24 hour diastolic BP and nocturnal diastolic BP in children aged 6–18 years [23]. Therefore, UA level, which can be elevated prior to the elevation of BP, can be a hypertension predictor.

The causal relationship between UA and hypertension in adolescents is based on the aforementioned evidence. Feig et al. enrolled five 14- to 17-year-old children with newly untreated essential hypertension, who were then treated with

allopurinol for one month. All five children showed decreased casual BP and ambulatory BP, and four of the five children were normotensive at the end of one month. All five children also showed a rebound in their BPs following discontinuation of therapy [24]. In another study, 30 newly diagnosed hypertensive adolescents with hyperuricemia were treated with allopurinol (200 mg twice per day). The results determined that allopurinol therapy normalizes the BP of 86% of the patients receiving active treatment in contrast to 3% in the placebo group [25]. Even in prehypertensive obese adolescents, urate-lowering therapy worked remarkably well.

UA and Prehypertension

According to the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, prehypertension is defined as a condition during which systolic BP ranges from 120 mm Hg to 139 mm Hg or diastolic BP ranges from 80 mm Hg to 89 mm Hg [26]. Prehypertension is an intermediate state of primary hypertension [9,27] and is identified as a strong predictor of future hypertension and cardiovascular disease [28]. A meta-analysis among Asian and Western individuals further revealed the role of prehypertension in increasing the risk of coronary heart disease and population-attributable risk; this meta-analysis also indicated that the proportion of coronary heart disease attributed to prehypertension in Asian and Western participants was 8.4% and 24.1%, respectively [29]. Thus, efforts on prehypertension are helpful to prevent hypertension.

Several epidemiologic studies reported that UA was associated with prehypertension [30,31]. For example, Wu et al. [32] described that serum UA was associated with prehypertension across gender and ethnic groups in northern and northeastern China. Another Chinese study demonstrated that the odds ratio for prehypertension was 1.36 in participants with UA ≥ 365 $\mu\text{mol/L}$ compared with those with UA < 215.9 $\mu\text{mol/L}$ after adjusting for many confounders [30]. Likewise, Syamala et al. from the National Health and Nutrition Examination Survey reported that the multivariable-adjusted odds ratio for prehypertension was 1.96 in US participants with UA of more than 356.9 $\mu\text{mol/L}$ compared with those with UA of less than 237.9 $\mu\text{mol/L}$ [31]. The Brazilian Longitudinal Study of Adult Health reached a similar conclusion in men [33]. Jiang et al. analyzed the risk of each UA quartile with the control group to illustrate the relationship of UA and prehypertension [34]. The ORs of the four quartiles were 1.00 (95% CI, 0.91–1.1), 1.14 (0.97–1.34), 1.76 (1.49–2.07), and 1.86 (1.57–2.19). These results strongly indicated the harmful effects of an UA level of more than 327 $\mu\text{mol/L}$. Thus far, limited interventional trials have been conducted in which UA-lowering agents were administered to individuals with prehypertension. In one study,

adolescent prehypertensive patients with obesity, 60 were allocated randomly to groups receiving allopurinol, probenecid, or placebo. This study determined that the group that received allopurinol and probenecid treatments had a significant decrease in both systolic and diastolic BPs compared with the control group [35]. Another pilot study was conducted on adult prehypertensive and overweight participants. Results of that study showed that allopurinol lowered clinic BP and increased the percentage number of dippers, which provided additional benefits over the traditional recommendation for BP control [36].

However, Vucak et al. [37] determined that no association existed between elevated serum UA level and prehypertension, and prediabetes was not excluded as a confounding factor in their study. Wu et al. [38] also failed to determine a significant link in study participants with prediabetes and diabetes but not in study participants with normal glucose tolerance. A Japanese cross-sectional study determined that serum triglycerides level may interfere with the relationship between UA and prehypertension [39]. This finding was the opposite of that of Vucak et al. [37]. These discrepancies raise the new question of whether many other metabolic factors interfere or modify this relationship. The complex and inseparable interaction between these metabolic factors makes determining the relationship difficult. Large well-controlled trials are needed in the future.

UA and Salt Sensitivity of BP

Salt has been linked to hypertension for many years. A heterogeneous BP response to changes in dietary salt intake, which is the phenomenon generally referred as salt sensitivity, is regarded as an intermediate phenotype of essential hypertension and is observed in both hypertensive patients and normotensive individuals [8]. Salt-sensitive individuals account for more than 50% of hypertensive patients or normotensive individuals with a positive history of hypertension, whereas individuals with a negative history account for only approximately 27% [40]. Several studies indicated that salt-sensitive individuals were confronted with severe target organ damage and high morbidity and mortality of cardiovascular disease in normotensive or hypertensive individuals [41]. We have followed a group of hypertensive children from Shaanxi Province for 18 years and determined that the systolic BP, diastolic BP, and morbidity of hypertension in the salt-sensitive group were significantly higher than those of the salt-resistant group; this finding indicated that salt sensitivity was a risk factor of hypertension [42]. Since 2005, salt sensitivity has been regarded as an early marker of damage caused by hypertension.

The association between UA and salt sensitivity of BP has been proposed for many years, but this area of research remains

in its infancy. Young nondipper hypertensive patients have been reported to have high UA levels [43], whereas circadian BP rhythm showed a nondipper pattern in patients with salt-sensitive hypertension or chronic kidney disease with the disappearance of nighttime BP drop [44]. The index of sodium sensitivity, as the main parameter of salt-sensitive hypertension, determined a strong positive relationship with serum UA level ($r=0.721$, $p<0.01$) [45]. Hyperuricemia may be involved in the pathogenesis of salt-sensitive hypertension; however, the exact role remains unknown. Dating back to 1990s, Johnson et al. developed a mild hyperuricemic model using uricase inhibitor. Over the 7 weeks of intervention with low salt diet, the elevation in BP was linearly related to the rise in UA ($r=0.75$) [46]. Using allopurinol and benzydaron or removing the oxonic acid had a great benefit to revert serum UA and BP to a normal state. This finding further emphasized that high UA can increase BP. Watanabe et al. adopted the same animal models and administered a 0.125% NaCl or 2% NaCl diet [4]. This study found that the elevation of BP was only observed in formally hyperuricemic rats after high salt diet, thereby strongly indicating an increase of salt sensitivity of BP in hyperuricemic rats [4]. Additionally, hyperuricemia has been found to be more common in men, which could be due to the protective role of female sex hormones; higher UA level predicts more profound damages in women [47]. These findings highlight the prominent role of female sex hormones on UA levels. One study also found female sex hormones had a beneficial influence on salt-sensitive hypertension [48]. We cannot determine whether the protective role on salt-sensitive hypertension of female sex hormones is through the regulation of UA or the inverse; however, a link between salt sensitivity of BP and UA remains possible.

Although the evidence for this link is limited, we can speculate about the possible mechanisms based on the available studies in experimental rats. These mechanisms indicated that mild hyperuricemia resulted in salt sensitivity and finally hypertension in two phases. The first phase was directly UA dependent and relatively salt resistant. Epidemiological observations, rodent models, and cell studies have shown that elevated UA activates renin-angiotensin-aldosterone system (RAAS) [49,50]. RAAS aggravates resistant artery constriction, particularly renal afferent arteriole presenting a stenosis of arteriolar lumen and abnormal collagen deposition, thereby resulting in a decrease in renal plasma flow and renal ischemia with renal injury and inflammatory infiltration. The expression of juxtaglomerular renin was also markedly increased, and its local effect accelerated the progress of renal damage and downregulated neuronal nitric oxide synthesis in macula densa [46,51–53]. Therefore, renal dysfunction contributed to the dysregulation of sodium excretion and augmented BP response to salt. *In vitro* studies showed that UA interfered with the insulin signal transduction. UA also inhibited endothelial

nitric oxide synthase phosphorylation and nitric oxide production and upregulated the expression of chemokines and adhesion molecules that aggregate local inflammation [54]. UA level also influences the thickness of carotid intima-media [55] and increase in vascular stiffness. Flow-mediated dilatation can result in profound impairment [56]. In addition, urate crystals can be deposited on arteries after autopsy. These scenarios ultimately result in vascular dysfunction, thereby promoting the progression of hypertension and vascular disease. Additionally, UA enters vascular smooth muscle cells (VSMCs) via the urate transporter 1, thereby resulting in the activation of kinases and nuclear transcription factors, cyclo-oxygenase 2 generation, production of growth factors (platelet derived growth factor) and inflammatory proteins (C-reactive protein, monocyte chemoattractant protein-1), VSMC proliferation, and inflammatory activation [57–59]. Thus, increased serum UA mediates the induction of perivascular inflammation and irreversible arteriosclerosis of vessels, endothelial dysfunction, activation of RAAS, and inhibition of NO synthesis. All these changes perpetuate hypertension and renal dysfunction.

The second phase is characterized by arteriopathy that persists despite UA removal [4]. Once a vascular lesion is established, salt-sensitivity can be driven by the development of preglomerular vascular disease. The UA-induced salt-sensitive hypertension persists despite the correction of serum UA levels [60]. In addition, endothelium is involved in the regulation of sodium homeostasis [61]. Endothelium dysfunction and renal arteriopathy synergistically result in the imbalance of sodium homeostasis. High plasma sodium concentration further aggravates UA-induced damages and promotes salt sensitivity [62,63], thereby forming a vicious cycle.

Conclusions

Recent research progress has provided several important new insights into the inextricable role of UA in the onset of primary hypertension, particularly in adolescent hypertension, prehypertension, and salt sensitivity of BP, which are the early and intermediate stages of primary hypertension. Considering the intimate relationship between UA and these pathological states, we should consider measures to alleviate the adverse effects of UA on these states by achieving early intervention of hypertension and by retarding its progression. These goals appear promising. However, it is still premature to consider UA-lowering drugs for the treatment of hypertension outside of a clinical trial context because of the side effects of currently available hypouricemic agents that are not favorable to the available antihypertensive agents. Nevertheless, the harmful effects of UA can still direct our clinical practice. We should pay attention at least to the hyperuricemic patients and choose suitable drugs for them, such as angiotensin-converting enzyme

inhibitors or angiotensin-receptor blockers, which can lower RAAS activity and prompt the excretion of UA while lowering BP. The greatest theoretical benefit of treating hyperuricemia in this context is the possibility that elevated UA may lead to irreversible microvascular changes. This possibility has been predicated based on the results of animal models, but not yet proven in humans. The possibility of preventing or significantly delaying permanent salt-sensitive hypertension needs considerable more scientific support before UA-lowering agents are added to routine clinical practice.

References:

- Burt VL, Whelton P, Roccella E J et al: Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension*, 1995; 25(3): 305–13
- Blicher M, Kruger R, Olesen T et al: Impact of metabolic, hemodynamic and inflammatory factors on target organ damage in healthy subjects. *J Hypertens*, 2015; 33(Suppl. 1): e118
- Sautin YY, Johnson RJ: Uric acid: The oxidant-antioxidant paradox. *Nucleosides Nucleotides Nucleic Acids*, 2008; 27(6): 608–19
- Watanabe S, Kang D H, Feng L et al: Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension*, 2002; 40(3): 355–60
- MacIsaac RL, Salatzki J, Higgins P et al: Allopurinol and cardiovascular outcomes in adults with hypertension. *Hypertension*, 2016; 67(3): 535–40
- Mehta T, Nuccio E, McFann K et al: Association of uric acid with vascular stiffness in the framingham heart study. *Am J Hypertens*, 2015; 28(7): 877–83
- Ofori SN, Odia OJ: Serum uric acid and target organ damage in essential hypertension. *Vasc Health Risk Manag*, 2014; 10: 253–61
- Weinberger MH: Salt sensitivity of blood pressure in humans. *Hypertension*, 1996; 27(3 Pt 2): 481–90
- Whelton PK, He J, Appel LJ et al: Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA*, 2002; 288(15): 1882–88
- Lauer RM, Clarke WR: Childhood risk factors for high adult blood pressure: the Muscatine Study. *Pediatrics*, 1989; 84(4): 633–41
- Zinner SH, Rosner B, Oh W et al: Significance of blood pressure in infancy. Familial aggregation and predictive effect on later blood pressure. *Hypertension*, 1985; 7(3 Pt 1): 411–16
- Loeffler LF, Navas-Acien A, Brady TM et al: Uric acid level and elevated blood pressure in US adolescents: National Health and Nutrition Examination Survey, 1999–2006. *Hypertension*, 2012; 59(4): 811–17
- Alper AJ, Chen W, Yau L et al: Childhood uric acid predicts adult blood pressure: The Bogalusa Heart Study. *Hypertension*, 2005; 45(1): 34–38
- Sundstrom J, Sullivan L, D'Agostino RB et al: Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. *Hypertension*, 2005; 45(1): 28–33
- Rovda I, Kazakova LM, Plaksina EA: Parameters of uric acid metabolism in healthy children and in patients with arterial hypertension. *Pediatratria*, 1990; (8): 19–22
- Torok E, Gyarfás I, Csukas M: Factors associated with stable high blood pressure in adolescents. *J Hypertens Suppl*, 1985; 3(3): S389–90
- Viazzi F, Antolini L, Giussani M et al: Serum uric acid and blood pressure in children at cardiovascular risk. *Pediatrics*, 2013; 132(1): e93–99
- Sun HL, Pei D, Lue KH et al: Uric acid levels can predict metabolic syndrome and hypertension in adolescents: A 10-year longitudinal study. *PLoS One*, 2015; 10(11): e143786
- Yildirim A, Keles F, Kosger P et al: Uric acid levels in normotensive children of hypertensive parents. *Int J Chronic Dis*, 2015; 2015: 747082
- Robinson RF, Batitsky DL, Hayes JR et al: Body mass index in primary and secondary pediatric hypertension. *Pediatr Nephrol*, 2004; 19(12): 1379–84
- Feig DI, Johnson RJ: Hyperuricemia in childhood primary hypertension. *Hypertension*, 2003; 42(3): 247–52
- Bobridge KS, Haines GL, Mori TA et al: Dietary fructose in relation to blood pressure and serum uric acid in adolescent boys and girls. *J Hum Hypertens*, 2013; 27(4): 217–24
- Jones DP, Richey PA, Alpert BS et al: Serum uric acid and ambulatory blood pressure in children with primary hypertension. *Pediatr Res*, 2008; 64(5): 556–61
- 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(8): 924–32
- Feig DI, Nakagawa T, Karumanchi S A et al: Hypothesis: Uric acid, nephron number, and the pathogenesis of essential hypertension. *Kidney Int*, 2004; 66(1): 281–87
- Chobanian AV, Bakris GL, Black HR et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*, 2003; 42(6): 1206–52
- Vasan RS, Larson MG, Leip EP et al: Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: A cohort study. *Lancet*, 2001; 358(9294): 1682–86
- Egan BM, Stevens-Fabry S: Prehypertension – prevalence, health risks, and management strategies. *Nat Rev Cardiol*, 2015; 12(5): 289–300
- Huang Y, Cai X, Liu C et al: Prehypertension and the risk of coronary heart disease in Asian and Western populations: A meta-analysis. *J Am Heart Assoc*, 2015; 4(2): pii: e001519
- Liang J, Xue Y, Zou C et al: Serum uric acid and prehypertension among Chinese adults. *J Hypertens*, 2009; 27(9): 1761–65
- Syamala S, Li J, Shankar A: Association between serum uric acid and prehypertension among US adults. *J Hypertens*, 2007; 25(8): 1583–89
- Wu J, Yan W H, Qiu L et al: High prevalence of coexisting prehypertension and prediabetes among healthy adults in northern and northeastern China. *BMC Public Health*, 2011; 11: 794
- Lotufo PA, Baena CP, Santos IS et al: Serum uric acid and prehypertension among adults free of cardiovascular diseases and diabetes: Baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Angiology*, 2016; 67(2): 180–86
- Jiang L, Mo D, Yang R et al: Joint effects of serum uric acid and body mass index on risk of prehypertension in Chinese population. *Clin Chim Acta*, 2015; 446: 1–5
- Soletsky B, Feig DI: Uric acid reduction rectifies prehypertension in obese adolescents. *Hypertension*, 2012; 60(5): 1148–56
- Madero M, Rodriguez CF, Jalal D et al: A pilot study on the impact of a low fructose diet and allopurinol on clinic blood pressure among overweight and prehypertensive subjects: A randomized placebo controlled trial. *J Am Soc Hypertens*, 2015; 9(11): 837–44
- Vucak J, Katic M, Bielen I et al: Association between hyperuricemia, prediabetes, and prehypertension in the Croatian adult population – a cross-sectional study. *BMC Cardiovasc Disord*, 2012; 12: 117
- Wu IH, Wu JS, Sun ZJ et al: Higher serum uric acid level increases risk of prehypertension in subjects with normal glucose tolerance, but not prediabetes and diabetes. *J Hum Hypertens*, 2016; 30(8): 479–82
- Kawamoto R, Tabara Y, Kohara K et al: Interaction between serum uric acid and triglycerides in relation to prehypertension in community-dwelling Japanese adults. *Clin Exp Hypertens*, 2014; 36(1): 64–69

Acknowledgments

YW is grateful to the China Scholarship Council (No: 201506280092) for a PhD fellowship.

Conflicts of interest

The authors declare that there is no conflict of interest.

40. Sharma AM: Salt sensitivity as a phenotype for genetic studies of human hypertension. *Nephrol Dial Transplant*, 1996; 11(6): 927–29
41. Weinberger MH, Fineberg NS, Fineberg SE et al: Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension*, 2001; 37(2 Pt 2): 429–32
42. Mu J, Zheng S, Lian Q et al: Evolution of blood pressure from adolescents to youth in salt sensitivities: a 18-year follow-up study in Hanzhong children cohort. *Nutr J*, 2012; 11: 70
43. Giallauria F, Predotti P, Casciello A et al: Serum uric acid is associated with non-dipping circadian pattern in young patients (30–40 years old) with newly diagnosed essential hypertension. *Clin Exp Hypertens*, 2016; 38(2): 233–37
44. Kimura G, Dohi Y, Fukuda M: Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovascular events. *Hypertens Res*, 2010; 33(6): 515–20
45. Radenkovic S, Kocic G, Stojanovic D et al: Sodium sensitive hypertension: Can it be assessed by measuring uric acid levels? *J Hypertens*, 2015; 33(Suppl. 1): e117
46. Mazzali M, Hughes J, Kim YG et al: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension*, 2001; 38(5): 1101–6
47. Fang JJ, Wu JS, Yang YC et al: High uric acid level associated with increased arterial stiffness in apparently healthy women. *Atherosclerosis*, 2014; 236(2): 389–93
48. Brinson KN, Rafikova O, Sullivan JC: Female sex hormones protect against salt-sensitive hypertension but not essential hypertension. *Am J Physiol Regul Integr Comp Physiol*, 2014; 307(2): R149–57
49. Kim IY, Lee DW, Lee SB et al: The role of uric acid in kidney fibrosis: experimental evidences for the causal relationship. *Biomed Res Int*, 2014; 2014: 638732
50. Feig DI: Uric acid and hypertension. *Semin Nephrol*, 2011; 31(5): 441–46
51. Zharikov S, Krotova K, Hu H et al: Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. *Am J Physiol Cell Physiol*, 2008; 295(5): C1183–90
52. Nakagawa T, Mazzali M, Kang D H et al: Hyperuricemia causes glomerular hypertrophy in the rat. *Am J Nephrol*, 2003; 23(1): 2–7
53. Mazzali M, Kanellis J, Han L et al: Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol*, 2002; 282(6): F991–97
54. Liang WY, Zhu XY, Zhang JW et al: Uric acid promotes chemokine and adhesion molecule production in vascular endothelium via nuclear factor-kappa B signaling. *Nutr Metab Cardiovasc Dis*, 2015; 25(2): 187–94
55. Caliskan M, Guven A, Ciftci O et al: Serum uric acid and carotid artery intima media thickness in patients with masked hypertension. *Acta Cardiol*, 2014; 69(4): 417–23
56. Sincer I, Kurtoglu E, Caliskan M et al: Significant correlation between uric acid levels and flow-mediated dilatation in patients with masked hypertension. *Clin Exp Hypertens*, 2014; 36(5): 315–20
57. Kang D H, Han L, Ouyang X et al: Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol*, 2005; 25(5): 425–33
58. Kang DH, Park SK, Lee IK et al: 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): 3553–62
59. Kanellis J, Watanabe S, Li J H 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): 1287–93
60. Johnson RJ, Rodriguez-Iturbe B, Nakagawa T et al: Subtle renal injury is likely a common mechanism for salt-sensitive essential hypertension. *Hypertension*, 2005; 45(3): 326–30
61. Olde Engberink RH, Rorije NM, Homan van der Heide JJ et al: Role of the vascular wall in sodium homeostasis and salt sensitivity. *J Am Soc Nephrol*, 2015; 26(4): 777–83
62. Paar M, Pavenstadt H, Kusche-Vihrog K et al: Endothelial sodium channels trigger endothelial salt sensitivity with aging. *Hypertension*, 2014; 64(2): 391–96
63. Korte S, Strater AS, Druppel V et al: Feedforward activation of endothelial ENaC by high sodium. *FASEB J*, 2014; 28(9): 4015–25