Research Article

Interleukin-6, uric acid, and electrolytes for the detection of endothelial dysfunction in pre-hypertensive and hypertensive patients

Santhi Tadi, Balu Mahendran K

Department of Biochemistry, Nimra Institute of Medical Sciences, Jupudi, Andhra Pradesh, India.

Correspondence to: Santhi Tadi, E-mail: ashoknshanthi@gmail.com

Received: Janaury 15, 2019; **Accepted:** Febraury 06, 2019

ABSTRACT

Background: Hypertension is a major public health problem and key risk factor of coronary artery diseases and other vascular complications. Inflammation plays a major role in endothelial dysfunction, early diagnosis and new therapeutic strategies dramatically declines vascular complications in developing countries. Hence, identification of inflammatory markers might be useful to develop specific therapeutic interventions to treat hypertension and endothelial dysfunction. **Objectives:** The main objective of present study was to explore interleukin-6 (IL-6) and uric acid levels in newly diagnosed pre-hypertensive and hypertensive cases compared with healthy volunteers and to correlate these levels with sodium and potassium levels. **Materials and Methods:** A total of 100 hypertensive patients with 35–45 years of the age group were selected (according to the Joint National Committee -8) for this study and 50 healthy volunteer age-matched subjects were selected as controls. Serum IL-6 was assessed by enzyme-linked immunosorbent assay and routine investigations were performed by ERBA EM-360 fully automated analyzer. **Results:** Serum IL-6 and uric acid levels were significantly increased in pre-hypertensive and hypertensive subjects compared with controls. Serum IL-6 and uric acid levels showed a significant positive correlation with body mass index, cholesterol, triglycerides, and sodium levels and negative correlation with potassium levels. **Conclusion:** Elevated levels of IL-6 and uric acid in pre-hypertension and hypertension indicate low-grade systemic inflammation. Regular monitoring and new specific therapeutic strategies to maintain these levels within normal range might be useful for normal vascular endothelial function and to reduce vascular complications in hypertensive patients.

KEY WORDS: Hypertension; Interleukin-6; Uric Acid; Electrolytes

INTRODUCTION

Hypertension is generally asymptomatic silent killer and major public health problem affecting more than billion people worldwide.[1] It is one of the key risk factors for endothelial dysfunction and cardiovascular diseases (CVD).[2] Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India.[3,4] Endothelium plays a major role in the regulation of vascular tone through the release of several vasorelaxing and vasoconstricting factors such as prostacyclin, nitric oxide (NO), and endothelium-derived hyperpolarizing factor.[5-7] Persistent hypertension causes endothelial dysfunction, which, in turn, develops atherosclerosis and leads to cardiovascular disease.[8,9]

Inflammation is a key factor in the development of hypertension and associated CVD.[10] Studies reported that various systems interact in uncertain ways to cause hypertension and it is also well-known fact inflammation which plays a key role in the initiation, progression, and clinical implication of hypertension.[11] It has become clear that

Access this article online	
Website: http://www.ijmsph.com	Quick Response code
DOI: 10.5455/ijmsph.2019.0823026012019001	

the immune system and inflammatory response are essential in the pathogenesis of hypertension. Many inflammatory markers such as C-reactive protein, cytokines, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and chemokines have been increased in hypertensive patients supporting the role of the pathogenesis of hypertension.[12] Recently, it has been recognized that inflammatory cytokines such as interleukin-6 (IL-6) contribute to endothelial dysfunction and vascular hypertrophy and fibrosis.[13] IL-6 is a 23.7-kDa pro-inflammatory cytokine, secreted by activated macrophages, endothelial cells, vascular smooth muscle cells (VSMC), and adipose tissue.[14] IL- 6 affects expression, activity of endothelial NO synthase (eNOS), nicotinamide adenine dinucleotide phosphate oxidase thus influences NO and superoxide levels which lead to oxidative stress.[15,16]

Uric acid is a metabolic end-product of purine metabolism. It is freely filtered in glomeruli of the kidney and approximately 90% of filtered uric acid is reabsorbed, and it has a considerable physiological role as antioxidant.[17,18] High levels of blood uric acid (hyperuricemia) are the major etiological factor of gout. Uric acid scavenges free radicals and protects the erythrocyte membrane from lipid peroxidation.[19] Recent studies reported that uric acid has been implicated in a number of chronic diseases such as metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, and chronic kidney disease.[20] Epidemiological studies reported that there was a strong association between cardiovascular disease and gout.[21,22] Uric acid induces VSMC proliferation mediated through mitogen-activated protein kinase (MAPKs) pathway and also has pro-inflammatory effects on vascular cells.[23] Uric acid induces chemokine monocyte chemoattractant protein-1 (MCP-1) by activating transcription nuclear factor κ-B, MAPKs, and cyclooxygenase-2 (COX-2).[24]

Serum sodium and potassium play an important role in the regulation of blood pressure (BP).[25] These electrolytes also play a role in intermediary metabolism, cellular function, enzyme activities, and electrical gradients.[26] Hence, the present study was aimed to evaluate IL-6 and uric acid levels in prehypertensive and hypertensive cases compared with healthy volunteers and to correlate these levels with electrolytes.

MATERIALS AND METHODS

A total of 100 newly diagnosed hypertensive patients of both the sexes aged between 35 and 45 years attending the Department of Medicine, Nimra Institute of Medical Sciences, Jupudi, Andhra Pradesh state, India, were selected for our study. The included hypertensive patients were divided into two groups according to the Eighth Joint National Committee (JNC-8) guideline: Group I (pre-hypertension) - 50 patients with systolic BP (120–139) or diastolic BP (80–89) and Group II (Hypertension) - 50 patients with systolic BP (≥140) or diastolic BP (≥90). The baseline characteristics such as age, gender, height, body weight, and waist and hip circumferences were collected. Patients with diabetes mellitus, other CVD, and renal dysfunction, chronic alcoholics, smokers, pregnant women, and patients on medication such as antioxidant supplements were excluded from the study. 50 healthy sex- and age-matched subjects were selected as controls.

The study was approved by the Institutional Human Ethics Committee, and informed consent was obtained from each subject before sample collection and general examination.

Measurement of BP

BP was measured using a Mercury Sphygmomanometer (Diamond, Mumbai, India) with the patients in a sitting position, legs uncrossed. After 5 min of rest in the sitting position, BP was measured on both arms and the higher of the two is taken into consideration. If the systolic and diastolic BP were in different categories, the higher of the two was used in the classification.

Biochemical Analysis

Fasting venous blood samples were obtained from the study subjects and samples were centrifuged at 3000 rpm for 15 min. Routine investigations such as glucose (glucose oxidase/peroxidase [GOD/POD]), serum cholesterol (cholesterol oxidase/POD), triglycerides (TGL) (glycerol phosphate oxidase [GPO]/POD), high-density lipoprotein (HDL) cholesterol (direct enzymatic), and low-density lipoprotein (LDL) cholesterol were calculated using Friedewald formula. Urea (urease method), creatinine (alkaline picrate method), bilirubin (Mod. Jendrassik and Grof's method), total protein (biuret method), albumin (bromocresol green method), globulin (calculation) alanine aminotransferase, asparatate aminotransferase, alkaline phosphatase (modified IFCC–UV Kinetic method), and uric acid (uricase-POD method) were analyzed by ERBA EM-360 fully automated analyzer with standardized protocols. Serum IL-6 was assessed by enzyme-linked immunosorbent assay. Electrolytes [Na+ and K+] (ion selective electrode method) was estimated using Ion Selective Electrode Analyzer, EasyLyte Analyzer.

Statistical Analysis

Statistical analysis carried out with SPSS 20.0 software and values were expressed as mean ± standard deviation, $P < 0.05$ was considered statistically significant. Pearson correlation test was used for correlation analysis.

RESULTS

The present study showed that body mass index (BMI) and waist: hip ratio are significantly increased in pre-hypertensive and hypertensive subjects compared with controls. Increased

total cholesterol, TGL, LDL cholesterol, and decreased HDL cholesterol levels were observed in hypertensive patients compared with controls, and also, there was a significant difference between in pre-hypertensive and hypertensive subjects. Significantly increased serum IL-6, uric acid, sodium, and decreased potassium levels were observed in hypertensive patients compared with controls, and there was also a significant difference between pre-hypertensive and hypertensive subjects. IL-6 and uric acid showed a significant positive correlation with BMI, cholesterol, TGL, and sodium levels and negative correlation with potassium levels [Tables 1 to 5]

DISCUSSION

Hypertension has a major influence on vascular endothelial function, and it is a key risk factor for CVD, ischemic stroke, and chronic kidney disease (CKD).[27] BP is coupled with structural changes in the arteries, altered renin–aldosterone, and increased responsiveness to sympathetic nervous system stimuli.[28] The present study showed that BMI and waist:hip ratio are significantly increased in pre-hypertensive and hypertensive subjects compared with controls. Obesity coupled with increased visceral and retroperitoneal fat raises BP by increased renal tubular reabsorption, impairing pressure natriuresis, volume expansion due to activation of the sympathetic nervous system, and renin-angiotensin-aldosterone system.[29,30] In addition, obesity increases the inflammatory cytokines and adipocytes can induce aldosterone synthesis in the adrenocortical gland in an endocrine fashion. Visceral obesity is associated with increased plasma aldosterone levels. Mainly aldosterone effects are mediated through mineralocorticoid receptor and it is involved in endothelial dysfunction.[31] Hypercholesterolemia increases angiotensin II (ANG II) type 1 receptor gene expression on VSMC and promotes the oxidized LDL in human coronary artery endothelial cells.[32] Studies reported that hypercholesterolemia contributes vasoconstrictor responses to ANG II and expression of several components of the RAS in tissues and

Table 1: Baseline characteristics in controls, pre-hypertensive subjects, and hypertensive subjects

Parameters	Controls (*n*=50)	Pre-hypertensive subjects (*n*=50)	Hypertensive subjects (*n*=50)
Age	38.9±3.2	40.1±0.4.1	39.6±5.3
Males (%)	72.8	80.7	67.6
Females (%)	27.2	19.3	32.4
Body mass index	24.2±1.3	27.8±1[a]*	28.06±2.79[b]*
Waist: hip ratio	0.91±0.06	0.94±0.08[a]#	0.95±0.03[b]*
Systolic BP (mm Hg)	114.4±5.6	133.2±5.8[a]*	159.0±11.9[b]*,[c]*
Diastolic BP (mm Hg)	74.4±3.1	84.1±4.1[a]*	98.8±7.6[b]*,[c]*

Data are expressed as mean±SD, *P<0.001, #P<0.05 was considered statistically significant. a: Comparison between control and pre-hypertensive subjects. b: Comparison between control and hypertensive subjects. c: Comparison between pre-hypertensive and hypertensive subjects. BP: Blood pressure, SD: Standard deviation

Table 2: Fasting plasma glucose, lipid profile, and liver profile parameters in controls, prehypertensive subjects, and hypertensive subjects

Parameters	Controls (*n*=50)	Pre-hypertensive subjects (*n*=50)	Hypertensive subjects (*n*=50)
FPG (mg/dl)	85.2±8.5	89.3±12.8	90.1±15.4
Serum cholesterol (mg/dl)	175.3±8.6	198.1±16.4[a]*	210.7±20.7[b]*,[c]#
Serum TGL (mg/dl)	105.6±17.5	162.8±26.4[a]*	178.9±34.6[b]*,[c]#
HDL cholesterol (mg/dl)	44.1±3.4	42.5±3.6a#	39.3±2.4[b]*,[c]*
LDL cholesterol (mg/dl)	121.6±9.6	136.8±23.2[a]*	151.1±28.4[b]*,[c]#
Total bilirubin (mg/dl)	0.73±0.04	0.75±0.09	0.89±0.03
Direct bilirubin (mg/dl)	0.18±0.04	0.18±0.06	0.20±0.07
AST (IU/L)	27.6±2.5	29.3±6.9	29.8±7.9
ALT (IU/L)	28.4±3.9	29.5±5.7	28.5±5.7
ALP (IU/L)	97.6±22.1	97.2±24.9	96.2±28.9
Total protein (g/dl)	7.2±0.5	7.3±0.9	7.0±1.3
Albumin (g/dl)	3.8±0.4	3.8±0.9	3.6±0.7
Globulin (g/dl)	3.1±0.3	3.3±0.9	3.2±1.4

Data are expressed as mean±SD, *P<0.001, #P<0.05 was considered statistically significant. a: Comparison between control and pre-hypertensive subjects. b: Comparison between control and hypertensive subjects. c: Comparison between pre-hypertensive and hypertensive subjects. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FPG: Fasting blood glucose, TGL: Triglycerides, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase

Table 3: Renal profile, electrolytes, and IL-6 levels in controls, pre-hypertensive subjects, and hypertensive subjects

Parameters	Controls (*n*=50)	Pre-hypertensive subjects (*n*=50)	Hypertensive subjects (*n*=50)
Serum urea (mg/dl)	24.6±5.3	25.8±6.4	25.6±5.9
Serum creatinine (mg/dl)	0.74±0.1	0.81±0.3	0.9±0.3
Serum sodium (mmol/L)	133.1±2.1	149.5±4.0[a]*	153.5±4.0[b]*,[c]*
Serum potassium (mmol/L)	4.9±0.3	3.5±0.6[a]*	3.4±0.9[b]*,[c]*
Serum uric acid (mg/dl)	4.8±0.8	7.4±1.4[a]*	8.7±1.4[b]*,[c]*
Interleukin-6 (pg/ml)	1.3±0.26	2.8±0.76[a]*	3.7±1.2[b]*,[c]*

Data are expressed as mean±SD, *P<0.001, #P<0.05 was considered statistically significant. a: comparison between control and pre-hypertensive subjects. b: comparison between control and hypertensive subjects. c: comparison between pre-hypertensive and hypertensive subjects. IL-6: Interleukin-6

Table 4: Correlation between serum IL-6 and measured parameters in pre-hypertensive patients and hypertensive subjects

Parameters	Pre-hypertension (Correlation coefficient-r)	Hypertension (Correlation coefficient-r)
Cholesterol	0.323*	0.307*
TGL	0.287*	0.398**
HDL	−0.198	−0.245
LDL	0.122	0.135
BMI	0.298*	0.532**
Waist: Hip ratio	0.219	0.312*
Systolic BP	0.185	0.420**
Diastolic BP	0.354*	0.632**
Sodium	0.323*	0.359**
Potassium	−0.289*	−0.432**
Uric acid	0.398**	0.598**

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). IL-6: Interleukin-6, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BP: Blood pressure, TGL: Triglycerides

Table 5: Correlation between uric acid and measured parameters in pre-hypertensive patients and hypertensive subjects

Parameters	Prehypertension (Correlation coefficient-r)	Hypertension (Correlation coefficient-r)
Cholesterol	0.219	0.327*
TGL	0.398**	0.539**
HDL	−0.213	−0.239
LDL	0.214	0.222
BMI	0.343*	0.489**
Waist: hip ratio	0.087	0.312*
Systolic BP	0.321*	0.418**
Diastolic BP	0.198	0.333*
Sodium	0.298*	0.398**
Potassium	−0.312*	−0.454**

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). BMI: Body mass index, TGL: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BP: Blood pressure

leads to atherosclerosis.[33] Hypercholesterolemia *ex vivo* vascular reactivity and *in vitro* cell studies reported that the activation of Nlrp3 inflammasome by cholesterol crystal stimulation causes endothelial dysfunction.[34]

Inflammatory cytokines play a pivotal role in endothelial dysfunction and vascular hypertrophy and fibrosis. The present study explored that serum IL-6 levels were significantly increased in Prehypertensive, hypertensive patients compared with controls and there was significant positive correlation with BMI, Cholestero,TGL, Uric acid, sodium levels and negative correlation with Potassium levels, and there were a significant positive correlation with BMI, cholesterol,TGL, uric acid, and sodium levels and negative correlation with potassium levels. IL-6 plays a role on endothelial activation, immune cell recruitment, vascular permeability, hypertrophy, and fibrosis.[35,36] Our findings suggest that inflammatory biomarkers are associated

with obesity and visceral fat as reported earlier.[37] Several experimental studies reported that RAS plays a key role in the pathogenesis of hypertension and it is also linked with inflammation.[38-40] Recently, animal studies suggested that IL-6 plays a significant role in mediating both inflammatories and it is released from vascular tissue in response to ANG II, and the effect of ANG II on IL-6 release is blocked by ANG II receptor blockers (ARBs).[41] IL-6 is identified as a predictor of cerebrovascular, cardiovascular risk, and peripheral artery disease.[42]

Hyperuricemia revealed to cause hypertension through pathways that involved in the reduction of eNOS enzyme in macula densa of the kidney, stimulation of RAS, and declined renal perfusion.[43] The present study showed that serum uric acid levels were significantly increased in hypertensive subjects compared with controls and there was a significant difference between pre-hypertensive and hypertensive subjects. Uric acid stimulates VSMC proliferation triggers renal microvascular disease and afferent arteriolopathy leading to increased BP.[44] In addition, in the present study, uric acid shown a significant positive correlation with IL-6, TGLs, and BMI. Hyperuricemia affects adipocytes by increasing MCP-1, decreased production of adiponectin that leads to obesity, and increased triglyceride levels and inflammation.[45,46] Hence, in this view, uric acid may play a pivotal role in inflammation, obesity, and hypertriglyceridemia.

Significantly increased serum sodium and decreased potassium levels were observed in pre-hypertensive and hypertensive subjects compared with controls. The distal convoluted tubules of the kidney perform a major role in the maintenance of BP by reabsorption of Na+ through Na+–Cl- cotransporter.[47] In addition, in the present study, serum IL-6 and uric acid showed a significant positive correlation with sodium and negative correlation with potassium. IL-6 association might be due to the inflammation as reported experimental study reports of immune cells in the amplification of salt-sensitive (SS) hypertension in Dahl SS rats.[48] Hyperuricemia causes salt sensitivity mediated by uric acid-induced smooth muscle cell proliferation, activation of MAPKs, stimulation of COX-2, and platelet-derived growth factor and leads to vascular diseases.[49] Decreased dietary intake of potassium and diuretics can diminish the body potassium levels which can also increase uric acid levels in the blood. Na+ gradient generated by basolateral Na+-K+-ATPase, initiates urate transporters for uric acid reabsorption.[50,51] Hence, in this view, increased sodium and decreased potassium may influence the hyperuricemia in the pathogenesis of hypertension.

Strengths and Limitations of the Study

Sampling approach and analysis were followed by standard protocols and supervised by a vigorous quality assurance. The limitation of the present study was mainly any other causal association exists between hypertension and discussed variables. Large cohort and follow-up studies are required to confirm these findings.

CONCLUSION

Elevated levels of IL-6 and uric acid in pre-hypertension and hypertension indicate low-grade systemic inflammation. Regular monitoring and new specific therapeutic strategies to maintain these levels within normal range might be useful for normal vascular endothelial function and to reduce vascular complications in hypertensive patients.

REFERENCES

1. Narayan KM, Ali MK, Koplan JP. Global noncommunicable diseases where worlds meet. N Engl J Med 2010;363:1196-8.
2. Alhawassi TM, Krass I, Pont LG. Hypertension in older persons: A systematic review of national and international treatment guidelines. J Clin Hypertens (Greenwich) 2015;17:486-92.
3. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, *et al*. Hypertension in India: A systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens 2014;32:1170-7.
4. Gupta R. Trends in hypertension epidemiology in India. J Hum Hypertens 2004;18:73-8.
5. Hill CE, Phillips JK, Sandow SL. Heterogeneous control of blood flow amongst different vascular beds. Med Res Rev 2001;21:1-60.
6. Félétou M, Vanhoutte PM. Endothelium-derived hyperpolarizing factor: Where are we now? Arterioscler Thromb Vasc Biol 2006;26:1215-25.
7. Busse R, Edwards G, Félétou M, Fleming I, Vanhoutte PM, Weston AH, *et al.* EDHF: Bringing the concepts together. Trends Pharmacol Sci 2002;23:374-80.
8. Schiffrin EL, Canadian Institutes of Health Research Multidisciplinary Research Group on Hypertension. Beyond blood pressure: The endothelium and atherosclerosis progression. Am J Hypertens 2002;15:115S-122S.
9. Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, *et al.* Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106:653-8.
10. Harrison DG, Marvar PJ, Titze JM. Vascular inflammatory cells in hypertension. Front Physiol 2012;3:128.
11. Peng H, Yang XP, Carretero OA, Nakagawa P, D'Ambrosio M, Leung P, *et al.* Angiotensin II-induced dilated cardiomyopathy in balb/c but not C57BL/6J mice. Exp Physiol 2011;96:756-64.
12. Didion SP. Cellular and oxidative mechanisms associated with interleukin-6 signaling in the vasculature. Int J Mol Sci 2017;18:e2563.
13. Virdis A, Dell'Agnello U, Taddei S. Impact of inflammation on vascular disease in hypertension. Maturitas 2014;78:179-83.
14. Zhang X, Liu RY, Lei Z, Zhu Y, Huang JA, Jiang X, *et al.* Genetic variants in interleukin-6 modified risk of obstructive sleep apnea syndrome. Int J Mol Med 2009;23:485-93.
15. Karbach S, Wenzel P, Waisman A, Munzel T, Daiber A. ENOS uncoupling in cardiovascular diseases the role of oxidative

stress and inflammation. Curr Pharm Des 2014;20:3579-94.
16. Dworakowski R, Alom-Ruiz SP, Shah AM. NADPH oxidase-derived reactive oxygen species in the regulation of endothelial phenotype. Pharmacol Rep 2008;60:21-8.
17. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol 2016;213:8-14.
18. 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.
19. Kellogg EW 3rd, Fridovich I. Liposome oxidation and erythrocyte lysis by enzymically generated superoxide and hydrogen peroxide. J Biol Chem 1977;252:6721-8.
20. Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, Rivard C, *et al.* Uric acid in metabolic syndrome: From an innocent bystander to a central player. Eur J Intern Med 2016;29:3-8.
21. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH, MRFIT Research Group. *et al.* Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med 2008;168:1104-10.
22. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA, *et al.* Hyperuricemia and coronary heart disease: A systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2010;62:170-80.
23. Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. J Biol Chem 1991;266:8604-8.
24. 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.
25. Hu G, Xu X, Liang X, Yang X, Zhang J, Simayi Z, *et al.* Associations of plasma atrial natriuretic peptide and electrolyte levels with essential hypertension. Exp Ther Med 2013;5:1439-43.
26. Lobo DN. Fluid, electrolytes and nutrition: Physiological and clinical aspects. Proc Nutr Soc 2004;63:453-66.
27. Cai G, Zhang B, Weng W, Shi G, Xue S, Song Y, *et al.* E-selectin gene polymorphisms and essential hypertension in Asian population: An updated meta-analysis. PLoS One 2014;9:e102058.
28. Pinto E. Blood pressure and ageing. Postgrad Med J 2007;83:109-14.
29. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: Interaction of neurohumoral and renal mechanisms. Circ Res 2015;116:991-1006.
30. Wofford MR, Hall JE. Pathophysiology and treatment of obesity hypertension. Curr Pharm Des 2004;10:3621-37.
31. Caprio M, Newfell BG, la Sala A, Baur W, Fabbri A, Rosano G, *et al.* Functional mineralocorticoid receptors in human vascular endothelial cells regulate intercellular adhesion molecule-1 expression and promote leukocyte adhesion. Circ Res 2008;102:1359-67.
32. Li D, Saldeen T, Romeo F, Mehta JL. Oxidized LDL upregulates angiotensin II Type 1 receptor expression in cultured human coronary artery endothelial cells: The potential role of transcription factor NF-kappaB. Circulation 2000;102:1970-6.
33. Daugherty A, Rateri DL, Lu H, Inagami T, Cassis LA. Hypercholesterolemia stimulates angiotensin peptide synthesis and contributes to atherosclerosis through the AT1A receptor. Circulation 2004;110:3849-57.
34. Zhang Y, Li X, Pitzer AL, Chen Y, Wang L, Li PL, *et al.* Coronary endothelial dysfunction induced by nucleotide oligomerization domain-like receptor protein with pyrin domain containing 3 inflammasome activation during hypercholesterolemia: Beyond inflammation. Antioxid Redox Signal 2015;22:1084-96.
35. Shoji M, Furuyama F, Yokota Y, Omori Y, Sato T, Tsunoda F, *et al.* IL-6 mobilizes bone marrow-derived cells to the vascular wall, resulting in neointima formation via inflammatory effects. J Atheroscler Thromb 2014;21:304-12.
36. Gomolak JR, Didion SP. Angiotensin II-induced endothelial dysfunction is temporally linked with increases in interleukin-6 and vascular macrophage accumulation. Front Physiol 2014;5:396.
37. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, *et al.* Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: The Framingham heart study. Circulation 2007;116:1234-41.
38. Brasier AR, Recinos A 3rd, Eledrisi MS. Vascular inflammation and the renin-angiotensin system. Arterioscler Thromb Vasc Biol 2002;22:1257-66.
39. Kranzhöfer R, Schmidt J, Pfeiffer CA, Hagl S, Libby P, Kübler W, *et al.* Angiotensin induces inflammatory activation of human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 1999;19:1623-9.
40. Mehta PK, Griendling KK. Angiotensin II cell signaling: Physiological and pathological effects in the cardiovascular system. Am J Physiol Cell Physiol 2007;292:C82-97.
41. Lee DL, Sturgis LC, Labazi H, Osborne JB Jr., Fleming C, Pollock JS, *et al.* Angiotensin II hypertension is attenuated in interleukin-6 knockout mice. Am J Physiol Heart Circ Physiol 2006;290:H935-40.
42. Miwa K, Tanaka M, Okazaki S, Furukado S, Sakaguchi M, Mochizuki H, *et al.* Association between interleukin-6 levels and first-ever cerebrovascular events in patients with vascular risk factors. Arterioscler Thromb Vasc Biol 2013;33:400-5.
43. 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.
44. 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.
45. 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.
46. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811-21.
47. Lavie CJ, Milani RV, Ventura HO, Cardenas GA, Mehra MR, Messerli FH, *et al.* Disparate effects of left ventricular geometry

and obesity on mortality in patients with preserved left ventricular ejection fraction. Am J Cardiol 2007;100:1460-4.
48. De Miguel C, Das S, Lund H, Mattson DL. T lymphocytes mediate hypertension and kidney damage in dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol 2010;298:R1136-42.
49. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, *et al*. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension 2002;40:355-60.
50. Bobulescu IA, Moe OW. Renal transport of uric acid: Evolving concepts and uncertainties. Adv Chronic Kidney Dis 2012;19:358-71.
51. Hyndman D, Liu S, Miner JN. Urate handling in the human body. Curr Rheumatol Rep 2016;18:34.

How to cite this article: Santhi Tadi, Mahendran KB. Interleukin-6, uric acid, and electrolytes for the detection of endothelial dysfunction in pre-hypertensive and hypertensive patients. Int J Med Sci Public Health 2019;8(3):248-254.

Source of Support: Nil, **Conflict of Interest:** None declared.