Association of Elevated Serum Lipoprotein(a), Inflammation, Oxidative Stress and Chronic Kidney Disease with Hypertension in Non-diabetes Hypertensive Patients

Surapon Tangvarasittichai¹ · Patcharin Pingmuanglaew² · Orathai Tangvarasittichai¹

Received: 29 September 2015 / Accepted: 20 January 2016 / Published online: 29 January 2016
© Association of Clinical Biochemists of India 2016

Abstract Hypertension is the most common cardiovascular risk factor. Lipoprotein(a) [Lp(a)], inflammation, oxidative stress and chronic kidney disease (CKD) exacerbate the response to tissue injury and acts as markers of the vascular disease, especially in glomerulosclerosis. We compared the clinical characteristics of 138 non-diabetes hypertensive women (ndHT) patients with 417 non-diabetes normotensive subjects and tested the association of hypertension with Lp(a), inflammation, CKD and oxidative stress by using multiple logistic regression. BP, BMI, waist circumference, creatinine, Lp(a), inflammation and malondialdehyde levels were significantly higher and CKD state in the ndHT patients ($p < 0.05$). Multiple logistic regression showed hypertension associated with increased Lp(a), inflammation, ORs and 95 % CIs were 2.52 (1.33, 4.80), 2.75 (1.44, 5.27) after adjusting for their covariates. Elevated serum Lp(a) and inflammation levels concomitants with increased oxidative stress and CKD were the major risk factors associated with hypertension and implications for the increased risk of HT and vascular disease.

Keywords Hypertension · Lipoprotein(a) · hs-CRP · Chronic kidney disease · Malondialdehyde

Introduction

A prothrombotic state and elevated serum lipoprotein(a) [Lp(a)] are the two emerging risk factors that are reciprocally related and contribute to cardiovascular consequences in hypertensive patients with early renal failure [1, 2]. Elevated Lp(a) has been demonstrated in patients with moderate impairment of renal function, suggesting that this lipoprotein contributes to the increased risk for atherosclerotic disease seen in hypertensive patients [3].

Lipoprotein(a) is an atherogenic particle, that is a LDL-like substance which structure is apolipoprotein(a) [Apo(a)] attached with disulfide bond to apolipoprotein B-100 on the LDL core [4]. Apo(a) is synthesized and secreted into the circulation by liver.

Elevated Lp(a) concentrations have been demonstrated as the risk factor for atherosclerosis [5] and thrombosis [6]. Moreover, there is a possible link between chronic kidney disease (CKD) with hypertension (HT) [7, 8]. HT is closely associated with progressive kidney dysfunction, manifested as glomerulosclerosis, interstitial fibrosis, proteinuria, and eventually declining glomerular filtration. Injury or activation of the endothelium by hemodynamic changes has been shown to result in increased local synthesis of angiotensinogen in the remnant rat kidney [9]. Increased angiotensin (Ang) II and pressure-induced oxidative stress alter mitochondria and electrolyte transport efficiency, which together with reduced kidney oxygen tension can cause tissue hypoxia. Hypoxia is a known stimulus for fibrogenesis, and fibrosis is a common clinical finding in patients with hypertensive kidney damage.

Observational and clinical studies have demonstrated that elevated blood pressure (BP) confers significantly higher risk of all causes of cardiovascular disease (CVD)

✉ Surapon Tangvarasittichai
surapon14t@yahoo.com

¹ Chronic Disease Research Unit, Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand

² Department of Community Occupational Family Medicine, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand

mortality, especially in those patients with diabetes mellitus [10]. More recent studies revealed an association of Lp(a) and HT, using the experimental to demonstrated that Lp(a) is able to generate essential HT by impairing the arterial endothelium-dependent dilation [4, 11].

Hypertension and dyslipidemia often occur together, but few studies have explored the relationship between serum Lp(a) levels and hypertension in non-diabetic subjects. We hypothesized that oxidative stress, proinflammatory factors, such as C-reactive protein (CRP), influence Lp(a) levels to cause cardiovascular diseases. We aimed to investigate the possible association of HT with increased serum Lp(a), CRP concentrations, oxidative stress and CKD in non-diabetes hypertensive patients.

Materials and Methods

Subjects

This cross-sectional study was performed as part of a Health Survey for hypertensive residents from January 2010 to January 2013. Five hundred and fifty five women subjects were randomly selected from three districts in Phitsanulok Province. A questionnaire survey was conducted by trained health workers about demographic characteristics, occupational, medical history of diabetes, hypertension, renal diseases, cancer, other diseases and smoking. We identified our participants as 417 non-diabetes normotensive subjects (as NorT-Gr) (age-range 47–63 years) and 138 non-diabetes HT subjects (ndHT) (age-range 49–63 years). We excluded the 154 subjects with known cancer, diabetes, end stage renal failure, history of cerebrovascular and/or coronary atherosclerotic disease, infection and any caused of life threatening diseases and smoking from the study. The study protocol was approved by the Ethical committees of Naresuan University. All participants provided written informed consent and agreed to participate and provide blood samples in the present study.

Anthropometric and Blood Pressure Measurement

Height, weight, and BP were measured and body mass index (BMI) was calculated. Waist circumference (WC) was measured at the midpoint between the rib cage and the top of lateral border of iliac crest during minimal respiration. BP was recorded as the mean value of at least two measurements of each participant on the same day using a Terumo digital blood pressure monitor (ES-P110).

Hypertension was defined as an average BP $\geq$ 140/90 mmHg or if the participant was taking antihypertensive medications or had been diagnosed with HT [12, 13].

Blood Sample Collection and Biochemical Determination

Fasting venous blood was collected from all participants. Plasma glucose (Glu), blood urea nitrogen (BUN), TC, TG and HDL-C were measured by enzymatic method. Serum creatinine concentration was determined based on the Jaffe reaction. LDL-C concentrations were calculated with Friedewald's formula in specimens with TG levels < 400 mg/dl.

Lipoprotein(a) Assay

Lipoprotein(a) was measured by using Immunoturbidimetric assay for the quantitative in vitro determination in human serum. The method has been standardized against a highly purified Lp(a) preparation which is used as an in-house master calibrator (data on file at Roche Diagnostics).

Highly Sensitive C-Reactive Protein (hs-CRP) Assay

Highly sensitive-CRP concentrations were determined by using latex-enhanced immunonephelometric assay on the Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) that has been standardized against the World Health Organization reference. The normal range of hs-CRP was <3.0 mg/l (<0.03 g/l). All biochemical analysis was performed on the Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) at the laboratory of Medical Technology, Faculty of Allied health Sciences.

Renal Function

All participants had no clinically identified renal organ damage, defined as a serum creatinine level lower than 106.0 μ mol/l (1.2 mg/dl) and serum BUN level lower than 7.14 mmol/l (20 mg/dl). Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation [14]. The formula is: $eGFR = 186 * [\text{plasma creatinine} - 1.154] * (\text{age}) - 0.203 * (0.742 \text{ if female}) * (1.210 \text{ if African-American})$. Five eGFR stages were used: Stage I was normal eGFR (≥ 90 ml/min/1.73 m²); Stage II was mildly eGFR (60–89 mL/min/1.73 m²); Stage III was moderately eGFR (30–59 ml/min/1.73 m²); Stage IV was severely eGFR (<30 ml/min/1.73 m²), and Stage V was end-stage renal disease: eGFR (<15 ml/min/1.73 m²). An eGFR lower

than 60 ml/min/1.73 m² (moderately eGFR) was defined as chronic kidney disease (CKD) [15].

Malondialdehyde (MDA) Assay

MDA level was determined in thawed serum samples by using the thiobarbituric acid substances (TBARS) assay, a spectroscopic techniques as in our previous report [16]. The method is based on the reaction of one molecule of MDA with 2 molecules of TBA to yield a pink chromophore with absorption maximum at 532 nm.

Statistical Analysis

All variables are expressed as median and interquartile range. The Mann–Whitney U test was used to estimate difference between groups. Spearman rank correlation was used to assess the bivariate correlation of Lp(a) with blood pressure and other biochemical variables. Odds ratios (OR) from logistic regression analysis were used to estimate the risk of hypertension associated with elevated Lp(a), oxidative stress and CKD. Tests were two-tailed, and a *p* value <0.05 was considered significant and the 95 % confidence intervals (CI) determined by using the SPSS version 13.0 (SPSS, Chicago, IL).

Results

Of these study participants, 138 (24.9 %) were obese and ndHT patients. We found that SystBP, DiastBP, WC, BMI, CT, MDA, Lp(a) and hs-CRP levels were significantly higher and eGFR level was lower in ndHT than NorT (*p* < 0.05) as shown in Table 1. Bivariate correlations showed that Lp(a) concentration was significantly correlated with Glu, CT, eGFR and MDA (*r* = 0.286, *p* < 0.001; *r* = 0.212, *p* = 0.018; *r* = −0.193, *p* = 0.032; *r* = 0.347, *p* < 0.001, respectively), hs-CRP concentration was significantly correlated with Age, SystBP, diastBP, BUN and MDA (*r* = 0.215, *p* = 0.017; *r* = 0.367, *p* < 0.001; *r* = 0.418, *p* < 0.001; *r* = 0.220, *p* = 0.014, *r* = 0.196, *p* = 0.024), eGFR was significantly correlated with Age and CT (*r* = −0.410, *p* < 0.001; *r* = −0.557, *p* < 0.001) in ndHT subjects and the correlation of the other variables were demonstrated in Table 2. Multiple logistic regression was used to calculate the association of hypertension with elevated Lp(a) and hs-CRP after adjusting for their covariates. Hypertension appeared to increase Lp(a) concentration, ORs and 95 % CIs were 2.52 (1.33, 4.80), Lp(a) concentration, ORs and 95 % CIs were 2.75 (1.44, 5.27), respectively for these measures, after adjusting for CKD, MDA, TG, HDL-C, WC and Age (Table 3).

Discussion

Our present study demonstrated that SystBP, DiastBP, WC, BMI, CT, Lp(a), hs-CRP were higher and eGFR level was lower in ndHT subjects. The correlations of hypertension with elevated Lp(a) levels, hs-CRP, renal insufficiency and increased oxidative stress partly explains the increased susceptibility to vascular disease in HT patients with renal insufficiency. It can be hypothesized that the atherogenic effect of Lp(a) might adversely affect the renal vasculature and aggravate renal function in these patients [1]. Alternatively, higher levels of Lp(a) and CRP in hypertensive patients might be simply explained by worse renal function. Our present study demonstrated no significant differences in the conventional lipid profile, but that may be because lipid lowering drugs are commonly prescribed medication for hypertensive patients in Thailand. Some patients may have had clinically silent vascular disease resulting from increased Lp(a), hs-CRP levels and oxidative stress, rather than by hypertension [17]. Thus, the increased concentrations of Lp(a), hs-CRP and decreased eGFR in the hypertensive patients could constitute a first pathological sign, in the absence of organ damages. Many factors in hypertensive milieu were linked to explain how oxidative events contribute to hypertension, including angiotensin II, aldosterone, cytokines and stimulate enzymes such as NADPH oxidases, uncoupled nitric oxide synthase and the mitochondria to produce reactive oxygen species (ROS) that contribute to hypertension [18]. Liao et al. [19] have demonstrated that mice angiotensin (Ang)II-induced hypertension is associated with an inflammatory response that may contribute to the development of renal damage via increased oxidative stress and inflammation. ROS in the vessel induces vasoconstriction, which subsequently causes sodium and volume retention in the kidney, concomitant with enhanced inflammatory responses to cause hypertension [19].

Oxidative vascular injury can promote endothelial permeability, which increases entry of lipoproteins to the subendothelial space, where they are oxidized and enhance inflammation [20]. Oxidative stress mediated cellular damage, injury [21] and modification increases the inhibitory effect of Lp(a) on plasminogen binding to cell surfaces, which could attenuate fibrinolytic activity by reduced the activation of plasminogen [22]. Inflammation exacerbates the response to tissue or endothelial cells injury and acts as a prognostic marker of the current ischemic event, to act as the acute phase reaction [23]. Elevated Lp(a) concentration seems to be genetically modulated, some metabolic abnormalities might influence its synthesis or catabolism, such as the acute-phase response, endocrine disorders, diabetes, liver and renal

Table 1 Comparison of the general characteristics of non-diabetes hypertensive patients and non-diabetes normotensive subjects

Variables	Hypertensive Gr (n = 138)	Normotensive Gr (n = 417)	p value
Age (years)	57.0 (49.0–63.0) ^a	56.0 (48.0–63.0) ^a	0.186
SystBP (mmHg)	148.0 (142.0–161.0)	124.0 (112.0–134.0)	<0.001
DiastBP (mmHg)	91.0 (85.0–96.0)	76.0 (69.0–83.0)	<0.001
WC (cm)	88.5 (82.0–94.0)	82.0 (75.0–91.0)	<0.001
BMI (kg/m ²)	25.4 (23.5–27.6)	23.7 (21.7–27.7)	<0.001
Glu (mmol/l)	5.42 (5.01–5.94)	5.34 (5.06–5.83)	0.694
Urea (mmol/l)	4.28 (3.21–6.07)	4.28 (3.57–5.36)	0.460
CT (μmol/l)	97.24 (70.72–97.24)	79.56 (61.88–88.4)	<0.001
TC (mmol/l)	5.91 (4.95–6.84)	5.81 (5.09–6.61)	0.399
TG (mmol/l)	1.45 (1.05–1.97)	1.40 (1.03–1.97)	0.673
HDL-C (mmol/l)	1.68 (1.46–1.97)	1.69 (1.45–2.01)	0.493
LDL-C (mmol/l)	3.50 (2.62–4.22)	3.26 (2.56–3.98)	0.147
Lp(a) (g/l)	0.341 (0.206–0.647)	0.247 (0.139–0.425)	<0.001
MDA (μmol/l)	6.50 (4.80–8.00)	4.10 (3.90–4.80)	<0.001
hs-CRP (g/l)	0.055 (0.034–0.074)	0.030 (0.014–0.036)	<0.001
eGFR (ml/min/1.73 m ²)	59.42 (58.11–76.06)	80.78 (65.9–95.8)	<0.001

^a Median and interquartile range**Table 2** Bivariate correlation between parameters in hypertensive subjects using Spearman rank correlation

Correlation between parameters		Correlation coefficient		Correlation between parameters		Correlation coefficient	
		r	p value			r	p value
Age	SystBP	0.197	0.029	SystBP	DiastBP	0.445	<0.001
	Glu	0.187	0.037		BUN	0.230	0.010
	BUN	0.212	0.018	DiastBP	TC	0.207	0.021
	LDL-C	0.182	0.043		hs-CRP	0.418	<0.001
	eGFR	−0.410	<0.001	WC	BMI	0.586	<0.001
Lp(a)	Glu	−0.289	<0.001		Glu	0.268	0.003
	CT	0.212	0.018		TG	0.202	0.018
	eGFR	−0.193	0.032	BUN	CT	0.201	0.025
	MDA	0.347	<0.001		TC	0.197	0.028
eGFR	Age	−0.410	<0.001		LDL-C	0.221	0.014
	CT	−0.557	<0.001	hs-CRP	Age	0.215	0.017
Glu	BUN	0.242	0.007		SystBP	0.367	<0.001
	TG	0.326	<0.001		DiastBP	0.418	<0.001
TC	TG	0.254	0.004		BUN	0.220	0.014
	HDL-C	0.306	0.001		MDA	0.196	0.024
	LDL-C	0.594	<0.001	TG	HDL-C	−0.250	0.005

failure [24]. The most important of Lp(a) feature is the well-established behavior as acute-phase reactant, which demonstrated by the presence of several interleukin-6 responsive elements within the apo(a) gene [25]. Oxidative damage also leads to an increase in transcription factor NF-κB activation and subsequently to the inflammatory proteins over expression [26]. Increased hs-CRP as the chronic subclinical inflammation is a component of the insulin resistance, metabolic syndrome, obesity, endothelial

dysfunction, hypertension, dyslipidemia and type 2 diabetes mellitus, all of these features are the cardiovascular risk factors often occur in this cluster [27]. Block et al. [28] demonstrated that CRP levels were significantly associated with oxidative stress. Furthermore, elevated hs-CRP levels are associated with the increased morbidity and mortality in patients with CVD [29]. In these hypertensive patients, Lp(a) might be implicated in glomerular injury. Lp(a) and oxidized Lp(a) have been shown to induce activation of

Table 3 Association of hypertension with model 1 elevated Lp(a), oxidative stress and CKD model 2 elevated hs-CRP, oxidative stress and CKD after adjusting for their covariates of the study population

Variables	Hypertension		
	OR	95 % CI	<i>p</i> value
<i>Model 1</i>			
Lp(a) ^a	2.52	1.33–4.80	0.005
CKD	6.89	3.88–12.25	<0.001
MDA	12.13	6.98–21.06	<0.001
TG	1.00	0.99–1.00	0.502
HDL-C	1.01	0.99–1.03	0.273
WC	1.05	1.02–1.08	0.001
Age	0.98	0.95–1.01	0.117
<i>Model 2</i>			
eCRP ^a	2.75	1.44–5.27	0.002
CKD	7.03	3.95–12.49	<0.001
MDA	12.48	7.17–21.74	<0.001
TG	1.00	0.99–1.01	0.544
HDL-C	1.01	0.99–1.03	0.246
WC	1.05	1.02–1.08	0.001
Age	0.93	0.95–1.00	0.117

^a Model after adjusted with CKD, MDA, TG, HDL-C, WC and Age

reactive oxygen metabolites in isolated rat glomeruli [27]. It can interact with Toll-like receptors, to promote vascular disease [30]. Lp(a) can be retained in the sub-intimal space of the arteries longer than LDL-C, with consequent greater atherogenicity [31]. In addition to glomerular injury, increased vascular tone in renal microvessels limits renal blood flow. Increased Ang II and pressure-induced oxidative stress alter mitochondria and electrolyte transport efficiency, which together reduce kidney oxygen tension and can cause tissue hypoxia. It is now evident that hemodynamic and metabolic factors work together to induce CKD. Our present study demonstrated that HT is strongly associated with increased oxidative stress, elevated hs-CRP, progressive kidney dysfunction and suggests it may be manifested as glomerulosclerosis and eventually declining glomerular filtration. Clinically, hypertensive end stage renal disease (ESRD) is more commonly observed in the presence of atherosclerosis and glomerulosclerosis compared with ESRD arising from other etiologies (such as nephrolithiasis, glomerulonephritis and polycystic kidney disease) [32].

Our present study also revealed an association between hypertension with increased Lp(a), hs-CRP, MDA and CKD. These may show the relevance of Lp(a) in early renal failure caused by arteriolar nephrosclerosis. Lp(a) levels were inversely correlated with eGFR and elevated Lp(a) levels were also observed in hypertensive

patients in the absence of clinical evidence for CVD, cerebrovascular, coronary artery and peripheral vascular disease.

Limitation

The present study is a cross sectional nature, data of female only and did not control for their menopause status or alcohol consumption.

Conclusion

Elevation of serum Lp(a), hs-CRP levels, oxidative stress and CKD are strongly associated with increased risk for development and progression of HT. Our data suggested that elevated Lp(a), hs-CRP levels, oxidative stress and CKD may act as contributors and serve as predictors for the incidence of hypertension.

Acknowledgments We sincerely thank Naresuan University and The Phitsanulok Provincial for financial support and also thank Mr. Sarawut Kooburat, MS Tientip Jankaet, and all co-workers for their blood collection and technical assistance. We sincerely thank who the patients participated in this study and Asst. Prof. Dr. Ronald A. Markwardt, Faculty of Public Health, Burapha University, for his critical reading and correcting of the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest to report.

References

1. Catena C, Novello M, Lapenna R, Baroselli S, Colussi G, Nadalini E, et al. New risk factors for atherosclerosis in hypertension: focus on the prothrombotic state and lipoprotein(a). *J Hypertens*. 2005;23:1617–31.
2. Sechi LA, Catena C, Casaccio D, Zingaro L. Lipoprotein(a), haemostatic variables, and cardiovascular damage in hypertensive patients. *J Hypertens*. 2000;18:709–16.
3. Sechi LA, Zingaro L, Catena C, Perin A, De Marchi S, Bartoli E. Lipoprotein(a) and apolipoprotein(a) isoforms and proteinuria in patients with moderate renal failure. *Kidney Int*. 1999;56:1049–57.
4. Scanu AM. Lipoprotein(a) and the atherothrombotic process: mechanistic insights and clinical implications. *Curr Atheroscler Rep*. 2003;5:106–13.
5. Terres W, Tatsis E, Pfalzer B, Beil FU, Beisiegel U, Hamm CW. Rapid angiographic progression of coronary artery disease in patients with elevated lipoprotein(a). *Circulation*. 1995;91:948–50.
6. Collaboration Emerging Risk Factors, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412–23.

7. He J, Whelton PK. Elevated systolic blood pressure as a risk factor for cardiovascular and renal disease. *J Hypertens Suppl.* 1999;17:S7–13.
8. Marcantoni C, Jafar TH, Oldrizzi L, Levey AS, Maschio G. The role of systemic hypertension in the progression of nondiabetic renal disease. *Kidney Int Suppl.* 2000;75:S44–8.
9. Lee LK, Meyer TW, Pollock AS, Lovett DH. Endothelial cell injury initiates glomerular sclerosis in the rat remnant kidney. *J Clin Invest.* 1995;96:953–64.
10. Gazzaruso C, Buscaglia P, Garzaniti A, Bonetti G, Savino S, Mariotti S, et al. Lipoprotein(a) plasma concentrations, apolipoprotein (a) polymorphism and family history of coronary heart disease in patients with essential hypertension. *J Cardiovasc Risk.* 1996;3:191–7.
11. Wildman RP, Sutton-Tyrrell K, Newman AB, Bostom A, Brockwell S, Kuller LH. Lipoprotein levels are associated with incident hypertension in older adults. *J Am Geriatr Soc.* 2004;52:916–21.
12. Joint National Committee. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med.* 1997;157:2413–46.
13. World Health Organization-International Society of Hypertension. World health organization-international society of hypertension guidelines for the management of hypertension. Guidelines subcommittee. *J Hypertens.* 1999;17:151–83.
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med.* 1999;130:461–70.
15. National Kidney Foundation, Kidney Disease Outcome Quality Initiative Advisory Board. Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Kidney disease outcome quality initiative.* *Am J Kidney Dis.* 2002;39:S1–246.
16. Tangvarasittichai S, Poonsub P, Tangvarasittichai O, Sirigulsatien V. Serum levels of malondialdehyde in type 2 diabetes mellitus Thai subjects. *Siriraj Med J.* 2009;61:20–3.
17. Catalano M, Perilli E, Carzaniga G, Colombo F, Carotta M, Andreoni S. Lp(a) in hypertensive patients. *J Hum Hypertens.* 1998;12:83–9.
18. Harrison DG, Gongora MC. Oxidative stress and hypertension. *Med Clin North Am.* 2009;93:621–35.
19. Liao TD, Yang XP, Liu YH, Shesely EG, Cavaasin MA, Kuziel WA, et al. Role of inflammation in the development of renal damage and dysfunction in angiotensin II-induced hypertension. *Hypertension.* 2008;52:256–63.
20. Sima AV, Stancu CS, Simionescu M. Vascular endothelium in atherosclerosis. *Cell Tissue Res.* 2009;335:191–203.
21. Narayanan D, Xi Q, Pfeffer LM, Jaggar JH. Mitochondria control functional Cav1.2 expression in smooth muscle cells of cerebral arteries. *Circ Res.* 2010;107:631–41.
22. Naruszewicz M, Giroux LM, Davignon J. Oxidative modification of Lp(a) causes changes in the structure and biological properties of apo(a). *Chem Phys Lipids.* 1994;67(68):167–74.
23. Chakraborty B, Vishnoi G, Goswami B, Gowda SH, Chowdhury D, Agarwal S. Lipoprotein(a), ferritin, and albumin in acute phase reaction predicts severity and mortality of acute ischemic stroke in north Indian patients. *J Stroke Cerebrovasc.* 2013;22:e159–67.
24. Lippi G, Guidi G. Lipoprotein(a): an emerging cardiovascular risk factor. *Crit Rev Clin Lab Sci.* 2003;40:1–42.
25. Lippi G, Braga V, Adami S, Guidi G. Modification of serum apolipoprotein A-I, apolipoprotein B and lipoprotein(a) levels after bisphosphonates-induced acute phase response. *Clin Chim Acta.* 1998;271:79–87.
26. Kwon HK, Hwang JS, So JS, Lee CG, Sahoo A, Ryu JH, et al. Cinnamon extract induces tumor cell death through inhibition of NF-kappa B and AP1. *BMC Cancer.* 2010;10:392–401.
27. de Ferranti SD, Rifai N. C-reactive protein: a nontraditional serum marker of cardiovascular risk. *Cardiovasc Pathol.* 2007;16:14–21.
28. Block G, Dietrich M, Norkus EP, Morrow JD, Hudes M, Caan B, et al. Factors associated with oxidative stress in human populations. *Am J Epidemiol.* 2002;156:274–85.
29. Greiber S, Kreusel M, Pavenstadt H, Schollmeyer P, Wanner C. Lipoprotein(a) induces glomerular superoxide anion production. *Nephrol Dial Transplant.* 1997;12:1330–5.
30. Bjorkbacka H. Multiple roles of toll-like receptor signaling in atherosclerosis. *Curr Opin Lipidol.* 2006;17:527–33.
31. Walton KW, Hitchens J, Magnani HN, Khan M. A study of methods of identification and estimation of Lp(a) lipoprotein and of its significance in health, hyperlipidaemia and atherosclerosis. *Atherosclerosis.* 1974;20:323–46.
32. Bleyer AJ, Chen R, D'Agostino RB Jr, Appel RG. Clinical correlates of hypertensive end-stage renal disease. *Am J Kidney Dis.* 1998;31:28–34.