Relationship between platelet count and platelet width distribution and serum uric acid 1 concentrations in patients with untreated essential hypertension

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Running title: Association of Uric-acid/PDW/PLT with HTN

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Abstract

Hematological parameters have emerged as independent determinants of high serum concentrations of uric-acid and predictive-factors in the evaluation of the total cardiovascular-risk in patients with essential-hypertensive. Here we have investigated the possible relationships between hematological-factors and serum uric-acid levels in hypertensive-patients recruited as part of Mashhad-Stroke and Heart-Atherosclerotic-Disorders cohort study. Two-thousand three-hundred and thirty four hypertensive individuals were recruited from this cohort and these were divided into two groups; those with either high or low serum uric acid concentrations. Demographic, biochemical and hematological characteristics of population were evaluated in all the subjects. Logistic-regression-analysis was performed to determine the association of hematological-parameters with hypertension. Of the 2334 hypertensive-subjects, 290 cases had low uric-acid, and 2044 had high serum uric acid concentrations. Compared with the low uric acid group, the patients with high serum uric acid, had higher values for several hematological parameters, whilst platelet counts (PLT) were lower. Multiple linear regression analysis showed that PLT and serum hs-CRP were correlated with serum uric acid level. Stepwise multiple logistic regression model confirmed that PDW and gender were independent determinant of a high serum uric acid. PDW and PLT appear to be independently associated with serum uric acid level in patients with hypertension.

Key word: Hypertension, PDW, uric acid, biomarker

Introduction

Hypertension (HTN) is one of the major risk factors of cardiovascular disease [1]. Recently Luo et al., showed that there is a significant positive association between hematological parameters and serum uric acid level in patients without antihypertensive treatment. hematological parameters were significantly different in hypertensive patients with high serum uric acid levels compared with those of low high uric acid level. Hematological parameters are suggested to be independent determinants of serum uric acid in newly diagnosed hypertensive[2]. Moreover, it is reported that some hematological parameters are correlated with higher systolic and diastolic blood pressures independently of age, inflammatory status and anemia [1].

Against this background, it has recently being suggested that uric acid is a risk factor for cardiovascular disease [3]. Uric acid is the end product of purine metabolism [4]. Hyperuricemia is defined as a serum concentration ≥7 mg/dL for men and ≥6 mg/dL for women. Increased serum uric acid is found in postmenopausal women, African-American patients with renal disease and is related to alcohol intake. Several other factors can influence the concentrations of uric acid, e.g. diet, obesity, and Metabolic Syndrome [5]. Moreover, it has been shown that an elevated serum uric acid is associated with an increased risk of CVD, all-cause mortality, and new-onset diabetes in hypertensive patients [4]. Hyperuricemia is also associated with the inflammatory process. Some inflammatory cytokines may activate xanthine oxidase enzyme in epithelial cells, causing serum uric acid to increase. The inflammatory status is also related to ineffective erythropoiesis, and it has been suggested that inflammatory cytokines, such as interleukin (IL)-1 β, IL-6, tumor necrosis factor (TNF)-α, desensitize bone marrow erythroid progenitors to erythropoiesis, inhibit red blood cell maturation and thereby promote anisocytosis [3].

Recently, the relationship between hematological indices, serum level of uric acid and hypertension have received new interest. The aim of the present study was to investigate the relationships between hematological factors, specifically hematological parameters, and serum uric acid concentrations in individuals with and without hypertension, recruited as part of the Mashhad Stroke and Heart Atherosclerotic Disorders (MASHAD) cohort study.

Methods

Population

In the current study, 2334 hypertensive individuals were recruited from the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study [6-7]. All participants providedinformed written consent. The study was approved by ethics committee of Mashhad University of Medical Sciences Mashhad, Iran.

Individuals were categorized based on blood pressure measurements and serum uric acid levels. Those who had systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg were defined as Hypertensive. Low (<4.8 μmol/L) and high (≥4.8 μmol/L) uric acid groups were defined based on serum uric acid concentration. Hence the patients were classified into 4 groups: non-hypertensive patients who had low level of serum uric acid, non-hypertensive patients who had high level of serum uric acid, hypertensive patients who had low level of serum uric acid, and hypertensive patients who had high level of serum uric acid. All methods were performed in accordance with the relevant guidelines and regulations and with approval of Mashhad university of Medical Sciences.

Anthropometric measurements:

Height, body weight, and waist circumference (WC) were measured as previously described [7-86,7]. Body Mass Index (BMI), systolic and diastolic blood pressures (BP) were evaluated as reported recently[9-10].

Biochemical parameters:

Serum levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), high sensitive C-reactive protein (hs-CRP), uric acid (UA), low-density lipoprotein cholesterol (LDL-C) and fasting blood glucose (FBG) were measured as previously described [11-138].

Hematological parameters:

Hematological indices including white blood cells count (WBC), red blood cells count (RBC), platelets count (PLT), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), red blood cell distribution width (RDW) and platelet distribution width (PDW) were measured using a Sysmex K800 automated cell counter (Sysmex Inc. United States), as described recently[14-16].

Statistical analysis:

Statistical Package for Social Sciences (SPSS; version 20 for Windows) was used to analyze data. Student's T-test and chi-squared test were used for understanding the differentiation between qualitative and quantitative variables, respectively. Pearson's correlation coefficients were counted between uric acid and other parameters. Continuous data are expressed as means ± Standard deviations (SD)[17]. P values below 0.05 were considered as statistically significant in all applied tests.

Results:

Demographic and clinical characteristics of the population:

Of the total number of 9749 subjects recruited into the MASHAD study, 2334 subjects with hypertension were identified of whom 290 had a low serum uric acid level and 2044 had a high serum uric acid. Demographic and clinical characteristics of the population are described in Table 1. We observed a significant difference for age, Sex, BMI, HDL, TG,

FBG, RBC, HGB, HCT, PLT, MCH and platelet size variability between groups defined by low/high uric acid (Table 1).

Correlation assessment in hypertensive patients:

Correlation analysis indicated that serum uric acid concentrations were positively related to hs-CRP, BMI, TG, MCH, WBC, RBC, HGB, HCT, cholesterol and age. An inverse relationship was found between serum uric acid and FBG, HDL-C, and PLT. These findings are described in Table 2-3.

Regression analysis for serum uric acid levels in hypertension patients:

The collinearity analysis showed that there are apparent multi-collinearities among variables. In a stepwise multiple linear regression analysis, age, gender, BMI, HDL-C, cholesterol, FBG, TG, hs-CRP, and PLT were statistically significant factors (Table 3). Multiple linear regression analysis for effects of independent variables on serum uric acid level in hypertensive patients are shown in Table 4. These data showed an association of age, gender, BMI, serum fasted cholesterol and triglycerides (TG), FBG, and PDW with serum uric acid in patients with untreated essential hypertension (Table 4).

Discussion

To the best of our knowledge this is the first cohort study evaluating and validating the association of hematological parameters, including WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT and platelet size variability (PDW) with serum uric acid concentrations in individuals with hypertension. Our findings showed a significantly positive association between hs-CRP, and PLT and serum uric acid level in patients without antihypertensive treatment. PLT and PDW were identified as independent determinants of a high serum uric acid in newly diagnosed hypertensive.

Hyperuricemia is an indirect indicator of increased oxidative stress. During the synthesis of uric acid, hydrogen peroxide is generated[18]. It is not known whether uric acid would be a

causal factor or an antioxidant protective response against oxidative stress. While chronic high uric acid concentrations are associated with an increased risk for coronary artery disease (CAD), acute elevations seem to provide antioxidant protection [5]. The increased serum uric acid levels in hypertensive patients may be due to the decline in renal blood flow that is associated with hypertension; reduced renal blood flow may be associated with a reduced urate excretion[18]. Several mechanisms have been proposed for the association between serum uric acid and cardiovascular and renal abnormalities, including: (1) increased uric acid production that may counteract oxidative stress and endothelial damage in the context of the atherosclerotic process; (2) the severity of hypertension itself; (3) a subtle reduction in glomerular filtration rate leading to impaired renal uric acid clearance[19]. Moreover it has been documented that higher WC and BMI are associated with higher insulin resistance and leptin production, and both reduce renal uric acid excretion, thus increasing its serum concentration. HDL-C concentration is negatively associated with insulin resistance, which in turn can influence its negative correlation to uric acid [5]. These data are in accord with our findings.

Furthermore we found a significant relationship between serum uric acid and serum hs-CRP in the hypertensive group. Ruggiero et al suggested that serum uric acid has positive relationship with inflammatory markers such as WBC, CRP, IL-6, IL-18, and TNF-α. Briefly, in inflammatory related diseases, chronic hypoxia causes cellular damage that upregulates the xanthine oxidase enzyme, leading to parallel increase of uric and free radical production, resulting into endothelial dysfunction[20]. Peng-Fei Li et al have shown that WBC and HGB are associated with metabolic syndrome[21], which is agreement with our data indicating that, WBC, and RBC were higher in hypertensive subjects compared to non-hypertensive ones. Additionally normocytic anemia is common among hypertensive patients. Lower hemoglobin concentrations were found in patients with uncontrolled than among those with well controlled hypertension, indicating a higher cardiovascular risk in uncontrolled

hypertension[22]. In this study HGB and HCT mean values did not differ significantly between hypertensive hyperuricemic subjects and non-hypertensive hyperuricemic subjects.

Of note we did not observe a significant association between RDW and uric acid. However, several other studies have suggested that RDW may be associated with vascular disorders, myocardial infarctions, stable angina, chronic heart failure, stroke, pulmonary thromboembolism, renal disease, malnutrition, neoplastic metastases to bone marrow and hypertension. In particular Tanindi et al., showed that RDW was higher in pre-hypertensive and hypertensive patients compared to healthy controls independently of age, inflammatory status and anemia. Moreover, higher RDW values were strongly correlated with higher systolic and diastolic blood pressures [1]. Min Luo et al. have shown that RDW may be a more sensitive indicator for predicting uric acid level than CRP [3]. However, in this study RDW was not correlated with serum uric acid level in hypertensive patients. This discrepancy can be explained at least in part by low sample size of most studies, ethnicity and possible influence of life style on hematological markers, although in the present study we explore the value of these markers in a large cohort study.

Increased platelet counts were reported in several studies in subjects with metabolic syndrome, atherosclerosis and CVD[34-36]. Additionally, several other studies have reported a relationship between PDW, MPV and PLT with blood pressure and hypertension [29], pulmonary arterial hypertension[37], pregnancy induced hypertension of preeclampsia, severe preeclampsia and eclampsia[30.] PDW shows the variation of the platelet size and May marker is more useful than MPV in providing platelet activity. Platelets play key roles in inflammation pathway via their activity to increase vascular permeability, atherosclerosis and cardiovascular events[39.40].

On the other hand, inconsistent results have reported by Luca and colleague that PDW had no significant association with the prevalence and development of CAD[31]. While other

studies showed an association between platelet size variability and serum uric acid in myocardial infarction[32] and neonatal sepsis[33]. Serum uric acid plays a key role to activate leukocyte and can lead to stimulation of inflammatory responses and to endothelial injury[33]. However,a positive association between increased uric acid levels and higher concentrations of inflammatory factors have been reported[39]. However, this is the first study demonstrating association of PDW with uric acid in patients with hypertensive that can be used as risk predictor of HTN.

We have found associations between age, gender, BMI, HDL-C, cholesterol, FBG, TG, hs-CRP, PLT and PDW with serum uric acid in hypertensive individuals. There was a significant relationship between serum uric acid level and hs-CRP in these patients, suggesting the role of inflammation in hypertension process. The possible interaction between blood viscosity, inflammation and uric acid, which in conjunction with high blood pressure may have an adverse impact on endothelial function and so become a risk factors for future events, which is in line with previous observation[24-28]. In particular Puddu et al., explored the association of serum uric acid with the incidence of coronary and cardiovascular events in an Italian population. They showed that increased serum uric acid levels and RBC was independently related with risk of CVD events in the 6-year follow-up of the Gubbio Study[24-25]. Another study by this research group also showed the value of serum uric acid as a predictor of long-term incidence of cardiovascular events and deaths[26]. In aggregate, further studies in prospective setting are warranted to explore the value of emerging marker as risk stratification factor.

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Table 1: demographic and clinical charateric of population			
	high uric acid(2044)	**low uric acid(290)**	**P-value**
Age (y)	52.19±7.96	50.91±7.60	0.01
Sex	Female: 903(44.2%) Male: 1140(55.8%)	Female: 54(19.9%) Male:218(80.1%)	<0.001
BMI (Kg/m^2)	29.38±4.70	28.44±4.60	0.002
Smoking status	No-smoker:1424(69.7%) Ex-smoker:234(11.4%) Current smoker: 386(18.9%)	No-smoker: 189(69.5%) Ex-smoker:33(12.1%) Current smoker:50(18.4%)	0.93
LDL (mg/dL)	120.29±37.50	119.71±33.25	0.8
HDL (mg/dL)	42.73±9.77	45.07±11.63	0.002
TG mg/ dL)	141(101-197)	109(78-143)	<0.001
Cholesterol	200.18±40.94	191.71±38.00	0.001
FBG (mg/dL)	98.65±42.48	118.47±63.91	<0.001
Hs-CRP	2.02(1.19-4.43)	1.63(1.11-3.71)	0.09
SBP (mm Hg)	145.56±19.42	145.63±16.63	0.95
DBP (mm Hg)	93.02±8.68	93.99±22.03	0.47
WBC(10^9/L)	6.23±1.55	6.09±1.54	0.17
RBC(10^{12}/L)	4.96±0.48	4.78±0.43	<0.001
HGB(g/dl)	13.96±1.53	13.35±1.59	<0.001
HCT(%)	41.92±3.77	40.41±4.93	<0.001
PLT(10^9/L)	229.54±62.39	246.46±71.36	<0.001
RDW(%)	41.49±3.07	41.32±2.83	0.34
PDW (%)	12.95±3.55	12.48±1.82	0.04
MCV(fl)	84.63±6.03	84.08±5.86	0.15
MCH(pg/cell)	28.29±2.35	27.91±2.72	0.03
MCHC(g/dl)	33.25±1.80	33.15±1.59	0.38

Table 2. Correlation coefficient between serum uric acid concentration and other variables in patients with untreated essential hypertension

	Correlation coefficient	**P value**
Age	0.06	0.002
BMI	0.09	<0.001
HDL-C	-0.13	0.001
FBG	-0.171	<0.001
TG	0.27	<0.001
LDL-C	-0.009	0.67
Cholesterol	0.09	<0.001
SBP	0.03	0.19
DBP	0.02	0.33
hs-CRP	0.08	<0.001
WBC	0.08	<0.001
RBC	0.17	<0.001
HGB	0.18	<0.001
HCT	0.20	<0.001
MCV	0.03	0.16
MCH	0.05	0.02
RDW	0.01	0.62
MCHC	0.007	0.74
PDW	0.03	0.19
PLT	-0.10	<0.001

Table 3. Stepwise multiple linear regression analysis for the effect of independent variables on serum uric acid				
	B	**S.E.**	**t**	**P value**
constant	3.16	0.303	10.33	<0.001
Age	0.012	0.003	3.48	0.001
Gender	-0.94	0.059	-15.97	<0.001
BMI	0.05	0.006	8.49	<0.001
HDL-C	-0.006	0.003	-2.07	0.04
Cholesterol	0.003	0.001	4.43	<0.001
FBG	-0.005	0.001	-8.49	<0.001
TG	0.003	0.000	10.66	<0.001
hs-CRP	0.012	0.003	4.067	<0.001
PLT	-0.001	0.000	-2.397	0.012

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Table 4. Stepwise multiple logistic regression for uric acid in patients with untreated essential hypertension						
	B	**S.E.**	**Wald**	**P value**	**Odd ratio**	**95%CI**
Age	0.022	0.01	5.40	0.02	1.02	1.004-1.042
Gender	1.27	0.2	39.49	<0.001	3.56	2.39-5.29
BMI	0.07	0.016	18.91	<0.001	1.07	1.04-1.11
Cholesterol	0.006	0.002	7.66	0.006	1.006	1.002-1.011
FBG	-0.012	0.001	77.035	<0.001	0.99	0.98-0.99
TG	0.009	0.001	35.82	<0.001	1.009	1.006-1.01
PDW	0.104	0.043	5.89	0.01	1.10	1.02-1.21
Constant	-6.44	2.34	7.56	0.006		

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