Research Communication

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

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Abbreviations: BP, blood pressure; BMI, body mass index; CVD, cardiovascular diseases; FBG, fasting blood glucose; HCT, hematocrit; hs-CRP, high sensitivity-c reactive protein; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; MASHAD, Mashhad Stroke and Heart Atherosclerotic Disorders; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PLT, platelet counts; PDW, platelet distribution width; HGB, hemoglobin concentration; RDW, red blood cell distribution width; RBC, red blood cells count; SD, standard deviations; TC, total cholesterol; TG, triglyceride; TNF, tumor necrosis factor; UA, uric acid; WC, waist circumference; WBC, white blood cells count

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Abstract

Hematological parameters have emerged as independent determinants of high serum concentrations of uric acid (UA) 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 UA 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 (HTN). Of the 2334 hypertensive subjects, 290 cases had low UA, and 2044 had high serum UA concentrations. Compared with the low UA group, the patients with high serum UA, had higher values for several hematological parameters, whilst platelet counts (PLT) were lower. Multiple linear regression analysis showed that PLT and serum high sensitivity-c reactive protein (hs-CRP) were correlated with serum UA level. Stepwise multiple logistic regression model confirmed that platelet distribution width (PDW) and gender were independent determinant of a high serum UA. PDW and PLT appear to be independently associated with serum UA level in patients with HTN. © 2018 BioFactors, 9999(9999):1–7, 2018

Keywords: *Hypertension; PDW; Uric Acid; Biomarker*

1. Introduction

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

Against this background, it has recently being suggested that UA is a risk factor for CVD [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 UA 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 UA, for example, diet, obesity, and Metabolic Syndrome [5]. Moreover, it has been shown that an elevated serum UA 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 UA 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 UA, and HTN have received new interest. The aim of this study was to investigate the relationships between hematological factors, specifically hematological parameters, and serum UA concentrations in individuals with and without HTN, recruited as part of the Mashhad Stroke and Heart Atherosclerotic Disorders (MASHAD) cohort study.

2. Methods

2.1. Population

In this study, 2334 hypertensive individuals were recruited from the MASHAD study [6,7]. All participants provided informed written consent. The study was approved by ethics committee of Mashhad University of Medical Sciences Mashhad, Iran.

Individuals were categorized based on BP measurements and serum UA levels. Those who had systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg were defined as Hypertensive. Low (<4.8 μmol/L) and high (≥4.8 μmol/L) UA groups were defined based on serum UA concentration. Hence, the patients were classified into four groups: nonhypertensive patients who had low level of serum UA, nonhypertensive patients who had high level of serum UA, hypertensive patients who had low level of serum UA, and hypertensive patients who had high level of serum UA. All methods were performed in accordance with the relevant guidelines and regulations and with approval of Mashhad university of Medical Sciences. Pregnant and breast feeding women, patients who had systemic disease, and patients taking any drug (including HTN-lowering drugs) were excluded from the study.

2.2. Anthropometric measurements

Height, body weight, and waist circumference (WC) were measured as previously described [8] body mass index (BMI),

systolic, and diastolic BP were evaluated as reported recently [9,10].

2.3. Biochemical parameters

Serum levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), high sensitive C-reactive protein (hs-CRP), UA, low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBG) were measured as previously described [11–13].

2.4. Hematological parameters

Hematological indices including white blood cells count (WBC), red blood cells count (RBC), platelet counts (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].

2.5. 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 UA 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.

3. Results

3.1. Demographic and clinical characteristics of the population

Of the total number of 9749 subjects recruited into the MASHAD study, 2334 subjects with HTN were identified of whom 290 had a low serum UA level and 2044 had a high serum UA. 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 UA (Table 1).

3.2. Correlation assessment in hypertensive patients

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

3.3. Regression analysis for serum UA levels in HTN patients

The collinearity analysis showed that there are apparent multicollinearities 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 UA 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 UA in patients with untreated essential HTN (Table 4).

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 UA concentrations in individuals with HTN. Our findings showed a significantly positive association between hs-CRP, and PLT and serum UA level in patients without antihypertensive treatment. PLT and PDW were identified as independent determinants of a high serum UA in newly diagnosed hypertensive.

Hyperuricemia is an indirect indicator of increased oxidative stress. During the synthesis of UA, hydrogen peroxide is generated [18]. It is not known whether UA would be a causal factor or an antioxidant protective response against oxidative stress. While chronic high UA concentrations are associated with an increased risk for coronary artery disease (CAD), acute elevations seem to provide antioxidant protection [5]. The increased serum UA levels in hypertensive patients may be due to the decline in renal blood flow that is associated with HTN; reduced renal blood flow may be associated with a reduced urate excretion [18]. Several mechanisms have been proposed for the association between serum UA and cardiovascular and renal abnormalities, including: (1) increased UA production that may counteract oxidative stress and endothelial damage in the context of the atherosclerotic process; (2) the severity of HTN itself; (3) a subtle reduction in glomerular filtration rate leading to impaired renal UA 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 UA excretion, thus increasing its serum concentration. HDL-C concentration is negatively associated with insulin resistance, which in turn can influence its negative correlation to UA [5]. These data are in accordance with our findings.

Furthermore we found a significant relationship between serum UA and serum hs-CRP in the hypertensive group. Ruggiero et al. suggested that serum UA 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]. Li et al. [21] have shown that WBC and HGB are associated with metabolic syndrome, which is agreement with our data indicating that, WBC, and RBC were higher in hypertensive subjects compared to nonhypertensive ones. Additionally normocytic anemia is common among hypertensive patients. Lower

TABLE 1 *Demographic and clinical charateric of population*

	High uric acid (2044)	*Low uric acid (290)*	P *value*
Age (years)	52.19 ± 7.96	50.91 ± 7.60	0.01
Sex	Female: 903 (44.2%)	Female: 54 (19.9%)	<0.001
	Male: 1140 (55.8%)	Male:218 (80.1%)	
BMI (kg/m^2)	29.38 ± 4.70	28.44 ± 4.60	0.002
Smoking status	No-smoker:1424 (69.7%)	No-smoker: 189 (69.5%)	0.93
	Ex-smoker:234 (11.4%)	Ex-smoker:33 (12.1%)	
	Current smoker: 386 (18.9%)	Current smoker:50 (18.4%)	
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

hemoglobin concentrations were found in patients with uncontrolled than among those with well controlled HTN, indicating a higher cardiovascular risk in uncontrolled HTN [22]. In this study, HGB and HCT mean values did not differ significantly between hypertensive hyperuricemic subjects and nonhypertensive hyperuricemic subjects.

Of note we did not observe a significant association between RDW and UA. 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 HTN. In particular, Tanindi et al. showed that RDW was higher in prehypertensive 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 BPs [1]. Luo et al. have shown that RDW may be a more sensitive indicator for predicting UA level than CRP [23]. However, in this study RDW was not correlated with serum UA 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

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	*SE*	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

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 [24–26]. Additionally, several other studies have reported a relationship between PDW, MPV, and PLT with BP and HTN [27], pulmonary arterial HTN [28], pregnancy induced HTN of preeclampsia, severe preeclampsia, and eclampsia [29]. 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 [30,31].

TABLE 4 *Stepwise multiple logistic regression for uric acid in patients with untreated essential hypertension*

	B	*SE*	*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		

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 [32]. While other studies showed an association between platelet size variability and serum UA in myocardial infarction [33] and neonatal sepsis [34]. Serum UA plays a key role to activate leukocyte and can lead to stimulation of inflammatory responses and to endothelial injury [34].

However, a positive association between increased UA levels and higher concentrations of inflammatory factors have been reported [30,40]. However, this is the first study demonstrating association of PDW with UA 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 UA in hypertensive individuals. There was a significant relationship between serum UA level and hs-CRP in these patients, suggesting the role of inflammation in HTN process. The possible interaction between blood viscosity, inflammation, and UA, which in conjunction with high BP may have an adverse impact on endothelial function and so become a risk factors for future events, which is in line with previous observation[35–40]. In particular, Puddu et al. explored the association of serum UA with the incidence of coronary and cardiovascular events in an Italian population. They showed that increased serum UA levels and RBC was independently related with risk of CVD events in the 6-year follow-up of the Gubbio Study [35,36]. Another study by this research group also showed the value of serum UA as a predictor of long-term incidence of cardiovascular events and deaths [37]. In aggregate, further studies in prospective setting are warranted to explore the value of emerging marker as risk stratification factor.

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Conflict of interest

The authors have no conflict of interest to disclose.

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