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The Association between Serum Uric Acid Level and Hematological parameters in Healthy Chinese Adults

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Abstract

Background: A definite and uniform standard concerning urate lowering therapy for hyperuricemic patients with different risks is lacking. It is important to identify simple and available clinical indicators to assess the risk of hyperuricemia and guide stratified treatment. The aim of the present study was to explore the association of serum Uric Acid (UA) levels with hematological parameters in healthy Chinese adults.

Case Presentation: In this retrospective study, 657 Chinese adults (447 males, 210 females) who underwent health check-up Huadong hospital affiliated to Fudan University in Shanghai, China were sampled. males, females and postmenopausal females older than 50 years (called female subgroup) were divided into three tertiles according to serum UA respectively. Clinical characteristics and hematological parameters were compared in different UA tertiles. Correlation and multiple regression analysis were used to investigate the relationship of UA with hematological parameters.

Results: After adjusting for potential confounding factors, serum UA was positively associated with RBC count, Hb and HCT in males. Serum UA was positively associated with MPV in females and postmenopausal females. RBC count, Hb and HCT were significantly higher in UA3 than that in UA1 in males. MPV was significantly higher in UA3 than that in UA1 in all females and postmenopausal females.

Conclusion: Our study demonstrated that serum UA was positively associated with RBC count, Hb and HCT in Chinese male adults and positively associated with MPV in Chinese female adults and postmenopausal females. Gender differences in the association between serum UA and MPV may not be related to estrogen levels. RBC count, Hb, HCT and MPV might assess the risk of hyperuricemia and guide stratified treatment.

Keywords: Serum Uric Acid; Hematological Parameters; Chinese; Hyperuricemia; Hypertension

Introduction

In recent decades, the prevalence of hyperuricemia has gradually increased with the change of living habits and diet styles, which is almost 13.3% in China [1], 11.9% in Western countries [2] and 21.4% in US at present [3]. Hyperuricemia has become one of the major problems that endanger global public health. A large scale of studies have indicated that hyperuricemia is a risk factor for the incidence and development of obesity, hypertension, diabetes, dyslipidemia, cardiovascular disease, kidney disease and stroke [4-7]. However, it was also evidenced that asymptomatic hyperuricemia was not an independent risk factor for cardiovascular disease or mortality. Hyperuricemia did associate with an increased risk of cardiovascular death only in participants with gout and existing cardiovascular disease [8]. It is quite possible that different patients with hyperuricemia may have different risks for gout or renal and cardiovascular complications. Thus, Japanese society of Gout and nucleic acid metabolism established a "Guideline for the Management of hyperuricemia and Gout" in 2002, a revised version in 2010, so as to manage hyperuricemia according to the presence or absence of gouty arthritis or tophi or complications [9]. However, this guideline is according to the already existed complications of hyperuricemia but not to potential risks. A definite and uniform standard concerning urate lowering therapy for hyperuricemic patients with different risks is lacking. It is important to identify simple and available clinical indicators to assess the risk of hyperuricemia and guide stratified treatment.

Hematological parameters that mainly include peripheral blood cell count and its related functional parameters are accessible in clinical practice. Many evidences reveal that several hematological parameters are associated with a variety of diseases, especially cardiovascular disease and kidney disease. Elevated White Blood Cell (WBC) count might predict the odds of future kidney function decline in Chinese population with normal basic kidney function [10]. Hemoglobin (Hb) is reported to be related to hypertension and arterial stiffness. Red blood cell volume Distribution Width (RDW) could be an effective predictive index in evaluating diabetes nephropathy [11] and early-stage renal function damage in essential hypertensive patients [12]. MPV is a predictive factor of stroke, Acute Myocardial Infarction (AMI) and restenosis of coronary angioplasty [13]. Uric acid stimulation might influce peripheral blood cell number and function to a certain extent. However, the relationship of serum UA with hematological parameters and gender differences have not been investigated in Chinese adults. Therefore, in this present study, we included healthy Chinese participants to explore the association between serum UA and hematological parameters in different genders.

Case Presentation

Study participants

In this retrospective study, 657 subjects (447 males, 210 females) who underwent routine health examinations from January 1, 2010 to September 30, 2015 at Huadong hospital affiliated to Fudan University (Shanghai, P.R.China) were included. Those who had cardiovascular disease (coronary artery disease, congestive heart failure and atrial fibrillation), renal dysfunction (eGFR<60 mL/min/1.73 m2), hepatic dysfunction, malignant tumour, hematologic disease, rheumatic disease and recent infection (pneumonia, urinary tract infection

and gastrointestinal infection) were excluded. Those who had taken UA-lowering drugs, such as benzbromarone, allopurinol or febuxostat were also excluded from this study. Our study was consented by the ethical review board of Huadong hospital affiliated to Fudan University and conformed to the ethics guidelines.

Biochemical measurements

Blood samples were collected in the morning after 12 hours of fasting and were then analyzed in the laboratory of Huadong hospital. Hematological parameters mainly include WBC count, neutrophil%, eosinophil%, basophil%, lymphocyte%, monocyte%, Red Blood Cell (RBC) count, Hb, HCT, Mean Corpuscular Volume (MCV), Mean corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), RDW, Platelet (PLT) count, MPV, Plateletcrit (PCT), Platelet Distribution Width (PDW). The serum levels of UA, Serum Creatinine (Scr), Erythrocyte Sedimentation Rate (ESR), High Sensitive C-Reactive Protein (hsCRP), Fasting Blood Glucose (FBG), postprandial 2-Hours Blood Glucose (2HBG), Fasting C-peptide (FC), postprandial 2-Hours C-Peptide (2HC), Fasting Insulin (FINS), postprandial 2-Hours Insulin (2HINS), Glycosylated Hemoglobin (HbA1c), Alkline Phosphatase (ALP), Total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Apolipoprotein A (ApoA), Apolipoprotein B (ApoB) and Estradiol (E2) were also measured. Both serum UA and Scr were measured by enzymatic methods. The estimated glomerular filtration rate (eGFR: milliliters per minute per 1.73 m^2), an index of renal function, was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [14]. Insulin Resistance (IR) was assessed by Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) that was calculated as fasting glucose (mmol/L) × fasting insulin (mIU/L) /22.5. Basic features, including body weight and body height, were also recorded. Body mass index (BMI) was calculated as the ratio of weight (kg) divided by height square (m^2).

Statistical analysis

Statistical analysis was performed using software SPSS version 17.0. The continuous clinical data were expressed as means ± Standard Deviation (SD). Males, females and postmenopausal females older than 50 years (called female subgroup) were divided into three tertiles respectively according to serum UA levels (UA1:UA<5.4 mg/dL, UA2:5.4 ≤ UA<6.7 mg/dL and UA3:UA ≥ 6.7 mg/dL for males; UA1:UA<4.5 mg/dL, UA2: 4.5 ≤ UA<5.4 mg/dL and UA3: UA ≥ 5.4 mg/dL for females; UA1:UA<4.5 mg/dL, UA2:4.5 ≤ UA<5.5 mg/dL and UA3:UA ≥ 5.5 mg/dL for female subgroup). The clinical characteristics and hematological parameters among each of the three UA tertiles were compared using one-way Analysis of Variance (ANOVA) if the data were distributed normally. If the data were non-normally distributed, we used rank-sum test among groups. In ANOVA, we used Least Significance Difference (LSD) test if the variance is homogeneous, and used Tamhane's T2 test if not. Pearson correlation or Spearman rank correlation were used to acquire hematological parameters and biochemical factors associated with serum UA levels. Multiple linear regression analysis was subsequently performed to analysis the relationship between serum UA levels and hematological parameters by adjusting for potential confounding variables. P<0.05 was considered to be statistically significant for all analyses.

Results

Clinical characteristics in three UA turtles in both genders

To exclude the confounders that might interact the effect of UA on hematological parameters, we firstly explored the effect of UA on the clinical characteristics. Clinical characteristics and comparisons of characteristics were detailed. BMI, Scr, eGFR, UA, FC, 2HC, FINS, 2HINS, HOMA-IR, TC, TG and ApoB differed significantly among three UA turtles in males (Table 1).

Variables	All males	UA1	UA2	UA3	P value
	(n=447)	(n=89)	(n=161)	(n=197)	
		UA<5.5 mg/dL	5.5 ≤ UA<6.7mg/dL	UA ≥ 6.7 mg/dL	
Age (years)	54.36 ± 8.12	56.13 ± 8.61	54.46 ± 7.90	53.48 ± 7.96	0.053
BMI (kg/m2)	25.41 ± 3.00	25.11 ± 3.32	24.94 ± 3.08	25.93 ± 2.71*	0.001
Scr (μmol/L)	78.11 ± 10.93	75.30 ± 11.17	77.43 ± 9.84	79.98 ± 11.37**	0.002
eGFR (mL/min/1.73 m^2)	92.27 ± 16.02	95.86 ± 17.11	92.70 ± 14.43	90.25 ± 16.48**	0.022
UA (mg/dL)	6.53 ± 1.27	4.81 ± 0.52	6.06 ± 0.33**	7.69 ± 0.79**	<0.001
ESR（mm/h）	10.09 ± 8.23	9.85 ± 9.22	9.94 ± 7.93	10.31 ± 8.07	0.677
hsCRP (mg/L)	1.43 ± 3.21	1.11 ± 1.09	1.31 ± 2.37	1.62 ± 4.09	0.233
FBG (mmol/L)	5.64 ± 1.30	5.78 ± 1.93	5.67 ± 1.29	5.55 ± 0.90	0.684
2HBG (mmol/L)	8.80 ± 3.25	9.20 ± 4.30	8.76 ± 3.11	8.64 ± 2.73	0.983
FC (ng/ml)	2.33 ± 1.01	2.11 ± 1.24	2.17 ± 0.82	2.56 ± 0.99**	<0.001
2HC (ng/ml)	8.22 ± 4.05	7.24 ± 4.03	8.35 ± 3.87*	8.60 ± 4.16**	0.018

FINS (mIU/L)	11.21 ± 6.26	10.42 ± 4.94	10.50 ± 7.02	12.21 ± 6.09*	0.001
2HINS (mIU/L)	58.24 ± 43.07	49.12 ± 39.77	59.93 ± 40.15*	61.29 ± 46.57*	0.048
HbA1c (%)	5.75 ± 0.68	5.91 ± 1.04	5.72 ± 0.61	5.69 ± 0.51	0.609
HOMA-IR	2.95 ± 2.36	2.81 ± 1.80	2.79 ± 2.89	3.15 ± 2.10	0.012
ALP (U/L)	65.33 ± 18.67	64.37 ± 16.46	66.14 ± 17.72	65.11 ± 20.37	0.362
TC (mmol/L)	4.66 ± 1.03	4.46 ± 1.02	4.59 ± 1.06	4.81 ± 0.99**	0.018
TG (mmol/L)	1.87 ± 1.35	1.48 ± 0.87	1.81 ± 1.51*	2.10 ± 1.35**	<0.001
HDL (mmol/L)	1.17 ± 0.27	1.17 ± 0.26	1.19 ± 0.27	1.15 ± 0.28	0.479
LDL (mmol/L)	2.71 ± 0.82	2.62 ± 0.81	2.70 ± 0.80	2.75 ± 0.84	0.437
ApoA (g/L)	1.24 ± 0.25	1.22 ± 0.24	1.25 ± 0.25	1.24 ± 0.25	0.616
ApoB (g/L)	1.35 ± 8.02	2.77 ± 17.82	1.03 ± 1.54	0.96 ± 0.23**	0.03
E2 (pmol/L)	159.41 ± 137.83	127.20 ± 74.47	172.79 ± 170.10	147.75 ± 71.98	0.786
* P <0.05, ** P <0.01 *vs* UA1.					

Table 1: Clinical characteristics and comparison of characteristics according to serum UA tertile in males.

Note: BMI: Body Mass Index; Scr: Serum Creatinine; eGFR: Estimated Glomerular Filtration Rate; ESR: Erythrocyte Sedimentation Rate; hsCRP: High sensitive C-Reactive Protein; FBG: Fasting Blood Glucose; 2HBG: 2-Hours Blood Glucose; FC: Fasting C-peptide; 2HC: 2-Hours C-peptide; FINS: Fasting Insulin; 2HINS: 2-Hours Insulin; HbA1c: Glycosylated hemoglobin; HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance, which was calculated as fasting glucose (mmol/L) × fasting Insulin (mIU/L)/22.5; ALP: Alkline Phosphatase; TC: Total Cholesterol; TG: Triglycerides; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; ApoA: Apolipoprotein A; ApoB: Apolipoprotein B; E2: Estradiol.

Age, BMI, Scr, eGFR, UA, ESR, FBG, FC, 2HC, FINS, 2HINS, HbA1c, HOMA-IR, ALP, TG, HDL and ApoA differed significantly among three UA turtles in females (Table 2).

Variables	**All females**	**UA1**	**UA2**	**UA3**	**P value**
	(n=210)	**(n=72)**	**(n=65)**	**(n=73)**	
		UA<4.5 mg/dL	**4.5 ≤ UA<5.4 mg/dL**	**UA ≥ 5.4 mg/dL**	
Age (years)	54.90 ± 8.53	51.92 ±7.97	55.28 ± 8.85*	57.51 ± 7.93**	<0.001
BMI (kg/m^2)	23.37 ± 3.18	22.22 ± 2.86	23.21 ± 2.77	24.62 ± 3.26**	<0.001
Scr (μmol/L)	58.53 ± 10.13	56.16 ± 11.14	59.90 ± 9.04*	59.75 ± 9.66*	0.043
eGFR (mL/min/1.73 m^2)	96.54 ± 19.96	103.33 ± 23.15	93.01 ± 16.36**	92.86 ± 17.76**	0.002
UA (mg/dL)	5.02 ± 1.06	3.94 ± 0.45	4.91 ± 0.25**	6.17 ± 0.69**	<0.001
ESR (mm/h)	16.27 ± 12.26	14.54 ± 11.34	14.11 ± 10.76	19.70 ± 13.60**	0.003
hsCRP (mg/L)	1.33 ± 2.18	1.10 ± 1.02	1.17 ± 0.94	1.59 ± 3.11	0.701
FBG (mmol/L)	5.18 ± 0.69	5.02 ± 0.64	5.05 ± 0.55	5.45 ± 0.77**	<0.001
2HBG (mmol/L)	8.34 ± 6.50	7.81 ± 2.55	9.18 ± 11.09	8.09 ± 2.60	0.709
FC (ng/ml)	2.29 ± 1.32	2.07 ± 1.53	2.05 ± 0.96	2.64 ± 1.34**	0.002
2HC (ng/ml)	7.78 ± 3.80	6.78 ± 4.15	7.47 ± 3.23	8.87 ± 3.70**	0.018
FINS (mIU/L)	10.17 ± 5.31	9.10 ± 4.48	9.63 ± 4.76	11.49 ± 6.11**	0.024
2HINS (mIU/L)	57.08 ± 39.91	51.31 ± 40.31	50.14 ± 35.38	67.87 ± 41.46*	0.031
HbA1c (%)	5.59 ± 0.57	5.50 ± 0.68	5.53 ± 0.36	5.73 ± 0.59**	<0.001

HOMA-IR	2.43 ± 1.46	2.08 ± 1.10	2.22 ± 1.24	2.88 ± 1.76**	0.004
ALP (U/L)	67.79 ± 20.71	60.04 ± 18.92	70.14 ± 20.70**	73.39 ± 20.36**	<0.001
TC (mmol/L)	5.06 ± 1.03	5.05 ± 0.93	5.01 ± 0.98	5.12 ± 1.17	0.804
TG (mmol/L)	1.31 ± 0.91	1.16 ± 1.13	1.32 ± 0.70**	1.46 ± 0.83**	<0.001
HDL (mmol/L)	1.42 ± 0.37	1.49 ± 0.37	1.48 ± 0.41	1.29 ± 0.31**	0.002
LDL(mmol/L)	2.95 ± 0.86	2.93 ± 0.77	2.88 ± 0.71	3.02 ± 1.04	0.61
ApoA (g/L)	1.39 ± 0.28	1.43 ± 0.29	1.43 ± 0.31	1.32 ± 0.22*	0.023
ApoB (g/L)	0.94 ± 0.24	0.92 ± 0.26	0.92 ± 0.21	0.97 ± 0.25	0.445
E2 (pmol/L)	178.01 ± 316.73	196.67 ± 263.90	267.61 ± 455.75	64.94 ± 128.48	0.133
* P <0.05, ** P <0.01 *vs* UA1.					

Table 2: Clinical characteristics and comparison of characteristics according to serum UA tertiles in females. **Note:** Abbreviations are the same as Table 1.

BMI, Scr, eGFR, UA, ESR, FBG, FC, HbA1c, HOMA-IR, ALP, TG, HDL and ApoA differed significantly among three UA tertiles in female subgroup (Table 3).

Variables	**Female subgroup**	**UA1**	**UA2**	**UA3**	**P value**
	(n=152)	**(n=38)**	**(n=56)**	**(n=58)**	
		UA<4.5 mg/dL	**4.5 ≤ UA<5.5 mg/dL**	**UA ≥ 5.5 mg/dL**	
Age (years)	58.73 ± 6.34	57.89 ± 5.64	58.96 ± 6.16	59.05 ± 6.98	0.688
BMI (kg/m^2)	23.93 ± 3.12	22.93 ± 3.15	23.65 ± 2.61	24.83 ± 3.35**	0.01
Scr (μmol/L)	58.66 ± 10.16	54.62 ± 10.83	61.14 ± 9.40**	58.94 ± 9.72*	0.01
eGFR (mL/min/1.73 m^2)	94.99 ± 20.43	104.39 ± 25.63	90.29 ± 17.01**	93.16 ± 17.58**	0.003
UA (mg/dL)	5.23 ± 1.05	3.98 ± 0.45	4.99 ± 0.30**	6.29 ± 0.70**	<0.001
ESR (mm/h)	17.12 ± 13.13	13.11 ± 12.14	16.14 ± 11.95	20.56 ± 14.02**	0.001
hsCRP (mg/L)	1.41 ± 2.34	1.34 ± 1.27	1.25 ± 0.92	1.58 ± 3.36	0.802
FBG (mmol/L)	5.31 ± 0.71	5.20 ± 0.74	5.13 ± 0.51	5.57 ± 0.79*	0.002
2HBG (mmol/L)	8.57 ± 7.11	8.10 ± 2.40	9.30 ± 11.46	8.20 ± 2.69	0.56
FC (ng/mL)	2.41 ± 1.37	2.29 ± 1.78	2.21 ± 1.16	2.65 ± 1.25*	0.02
2HC (ng/mL)	8.08 ± 3.79	7.23 ± 4.22	7.53 ± 3.27	9.07 ± 3.77	0.06
FINS (mIU/L)	10.64 ± 5.65	9.97 ± 5.17	9.80 ± 5.02	11.79 ± 6.31	0.113
2HINS (mIU/L)	60.46 ± 39.81	58.67 ± 39.04	54.04 ± 40.15	67.31 ± 39.75	0.215
HbA1c (%)	5.70 ± 0.59	5.70 ± 0.78	5.59 ± 0.35	5.79 ± 0.63	0.026
HOMA-IR	2.57 ± 1.55	2.32 ± 1.26	2.27 ± 1.26	2.99 ± 1.85	0.035
ALP (U/L)	71.88 ± 21.46	63.15 ± 21.83	74.04 ± 21.17*	75.50 ± 20.25**	0.015
TC (mmol/L)	5.16 ± 1.03	5.19 ± 0.82	5.05 ± 1.00	5.24 ± 1.19	0.596
TG (mmol/L)	1.33 ± 0.75	1.05 ± 0.61	1.35 ± 0.64**	1.51 ± 0.88**	0.001
HDL (mmol/L)	1.39 ± 0.36	1.49 ± 0.38	1.45 ± 0.36	1.27 ± 0.31**	0.003
LDL (mmol/L)	3.03 ± 0.88	3.04 ± 0.74	2.91 ± 0.71	3.15 ± 1.09	0.355

ApoA (g/L)	1.40 ± 0.28	1.46 ± 0.30	1.44 ± 0.31	1.31 ± 0.22*	0.013
ApoB (g/L)	0.95 ± 0.24	0.93 ± 0.26	0.92 ± 0.19	1.00 ± 0.26	0.123
E2 (pmol/L)	36.49 ± 48.60	37.87 ± 59.36	37.18 ± 43.69	34.59 ± 45.98	0.772
Note: * P <0.05, ** P <0.01 vs UA1.					

Table 3: Clinical characteristics and comparison of characteristics according to serum UA tertiles in female subgroup. **Note:** Abbreviations are the same as Table 1.

means the degree of change in hematological parameters per 1 mg/dL of serum UA increase; SE, standard error. HbA1c (r=0.197, P=0.017),

Relationship between the serum UA levels and hematological parameters

Pearson correlation, Spearman rank correlation analysis showed that serum UA levels were positively associated with BMI (r=0.153, P=0.001), Scr (r=0.174, P<0.001), FC (r=0.273, P<0.001), 2HC (r=0.162, P=0.002), FINS (r=0.166, P=0.002), HOMA-IR (r=0.131, P=0.013), TC (r=0.157, P=0.001), TG (r=0.281, P<0.001) and ApoB (r=0.137, P=0.004) in males. Serum UA levels were negatively associated with age (r=-0.146, P=0.002) and eGFR (r=-0.131, P=0.006) in males.

Serum UA levels were positively associated with age (r=0.250, P<0.001), BMI (r=0.380, P<0.001), ESR (r=0.238, P=0.001), FBG (r=0.306, P<0.001), FC (r=0.307, P<0.001), 2HC (r=0.267, P=0.001), FINS (r=0.262, P=0.001), 2HINS (r=0.209, P=0.012), HbA1c (r=0.332, P<0.001), HOMA-IR (r=0.313, P<0.001), ALP (r=0.282, P<0.001) and TG (r=0.281, P<0.001) in females. Serum UA levels were negatively associated with eGFR (r=-0.192, P=0.006), HDL (r=-0.240, P<0.001), ApoA (r=-0.146, P=0.038) and E2 (r=-0.225, P=0.024) in females.

Serum UA levels were positively associated with BMI (r=0.309 P<0.001), ESR (r=0.320, P<0.001), FBG (r=0.266, P=0.001), FC (r=0.289, P=0.001), 2HC (r=0.256, P=0.005), FINS (r=0.218, P=0.004), HOMA-IR (r=0.258, P=0.004), ALP (r=0.199, P=0.015) and TG (r=0.283, P<0.001) in female subgroup. Serum UA levels were negatively associated with eGFR (r=-0.195, P=0.038), HDL (r=-0.231, P=0.004) and ApoA (r=-0.182, P=0.028) in female subgroup. These indicators were considered as confounding factors for UA on hematological parameters.

Serum UA levels were positively associated with WBC count (r=0.113, P=0.017), RBC count (r=0.154, P=0.001), Hb (r=0.161, P=0.001) and HCT (r=0.165, P<0.001) in males before adjusting for the confounding factors. Serum UA levels were positively associated with WBC count (r=0.136, P=0.049), RBC count (r=0.246, P<0.001), Hb (r=0.240, P<0.001), HCT (r=0.256, P<0.001), MPV (r=0.176, P=0.01) and negatively associated with neutrophil% (r=-0.139, P=0.045) in females before adjusting for confounders. Serum UA levels were positively associated with RBC (r=0.217, P=0.007), Hb (r=0.202, P=0.012), HCT (r=0.240, P=0.003) and MPV (r=0.253, P=0.002) in female subgroup before adjusting for confounders.

After adjusting for confounding factors in three models in males (model 1 adjusted for age and BMI; model 2 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, 2HC, FINS and HOMA-IR; model 3 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, 2HC, FINS, HOMA-IR, TC, TG and ApoB), the association between serum UA and RBC count, Hb, HCT were still statistically significant, while the relationship of UA with

	Model 1			Model 2			Model 3		
	B	SE	P	B	SE	P	B	SE	P
WBC	0.119	0.049	0.015	0.165	0.075	0.03	0.118	0.076	0.121
RBC	0.033	0.013	0.013	0.052	0.018	0.005	0.052	0.019	0.007
Hb	1.052	0.377	0.005	1.428	0.532	0.008	1.406	0.544	0.01
HCT	0.308	0.106	0.004	0.382	0.148	0.011	0.386	0.153	0.012

Table 4: Multiple linear regression analysis for the associations between serum UA (independent variable) and hematological parameters (dependent variables) in different models in males.

Note: Model 1 adjusted for age and BMI; model 2 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, 2HC, FINS and HOMA-IR; model 3 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, 2HC, FINS, HOMA-IR, TC, TG and ApoB. B, unstandardized coefficient that WBC count disappeared (Table 4).

After the adjustment of confounders in females (model 1 adjusted for age and BMI; model 2 adjusted for age, BMI, ESR, hsCRP and eGFR; model 3 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, HbA1c, HOMA-IR, ALP, TG, HDL, ApoA and E2), the association between serum UA and MPV remained statistically significant (Table 5).

	Model 1			Model 2			Model 3		
	B	SE	P	B	SE	P	B	SE	P
WBC	0.169	0.089	0.06	-	-	-	-	-	-

NEUT%	-1.134	0.613	0.065	-	-	-	-	-	-
RBC	0.068	0.022	0.002	0.087	0.03	0.004	0.005	0.072	0.945
Hb	1.583	0.63	0.013	2.096	0.832	0.013	-0.968	1.995	0.631
HCT	0.506	0.179	0.005	0.612	0.246	0.015	-0.11	0.586	0.853
MPV	0.21	0.076	0.006	0.25	0.093	0.008	0.435	0.181	0.023

Table 5: Multiple linear regression analysis for the associations between serum UA (independent variable) and hematological parameters (dependent variables) in different models in females.

Note: Model 1 adjusted for age and BMI; model 2 adjusted for age, BMI, ESR, hsCRP and eGFR; model 3 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, HbA1c, HOMA-IR, ALP, TG, HDL, ApoA and E2. B, unstandardized coefficient that means the degree of change in hematological parameters per 1 mg/dL of serum UA increase; SE, standard error.

After the adjustment of confounders in female subgroup (model 1 adjusted for age and BMI;model 2 adjusted for age, BMI, ESR, hsCRP and eGFRmodel 3 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, HbA1c, HOMA-IR, ALP, TG, HDL, ApoA and E2), the relationship between serum UA and MPV remained (Table 6).

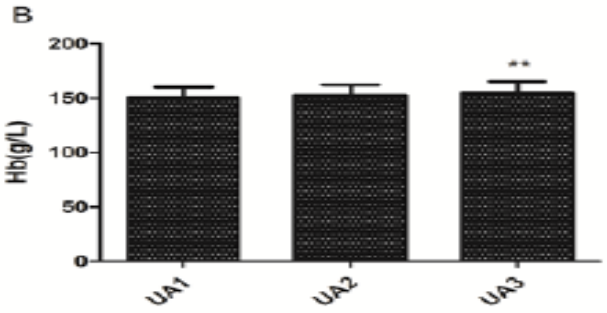

Figure 2: Comparison of Hb, according to serum UA tertiles in males.

	Model 1			Model 2			Model 3		
	B	SE	P	B	SE	P	B	SE	P
RBC	0.055	0.024	0.023	0.084	0.034	0.015	0	0.067	0.997
Hb	1.261	0.709	0.077	-	-	-	-	-	-
HCT	0.462	0.198	0.021	0.63	0.288	0.032	-0.17	0.602	0.78
MPV	0.25	0.084	0.004	0.339	0.114	0.004	0.468	0.188	0.021

Table 6: Multiple linear regression analysis for the associations between serum UA (independent variable) and hematological parameters (dependent variables) in different models in female subgroup.

Note: Model 1 adjusted for age and BMI; Model 2 adjusted for age, BMI, ESR, hsCRP and eGFR; Model 3 adjusted for age, BMI, ESR, hsCRP, eGFR, FC, HbA1c, HOMA-IR, ALP, TG, HDL, ApoA and E2. B, unstandardized coefficient that means the degree of change in hematological parameters per 1 mg/dL of serum UA increase; SE, standard error.

Hematological parameters in different UA tertiles

One-way ANOVA analysis revealed that RBC count, Hb and HCT in UA3 were significantly higher than that in UA1 in males. MPV in UA3 was significantly higher than that in UA1 in females and female subgroup (Figures 1-3).

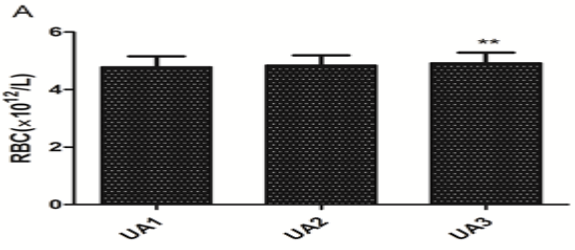

Figure 1: Comparison of RBC count, according to serum UA tertiles in males.

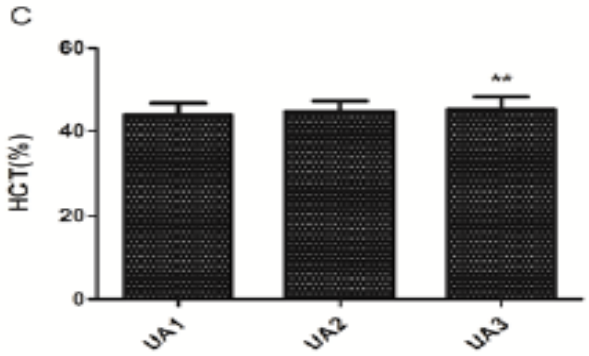

Figure 3: Comparison of HCT, according to serum UA tertiles in males.

Discussion

In this retrospective study, we explored the relationship of serum UA with hematological parameters and gender differences in healthy Chinese adults. The results indicated that serum UA was positively associated with RBC count, Hb and HCT in males and positively associated with MPV in females and postmenopausal females after adjusting for a variety of potential confounding factors. Gender differences in the association between serum UA levels and MPV may not be related to estrogen levels. RBC count, Hb, HCT and MPV might assess the risk of hyperuricemia and guide stratified treatment.

Hyperuricemia was positively associated with IR. IR is a prominent feature of a serious of metabolic disorders, including obesity, hypertension, diabetes mellitus, dyslipidemia and atherosclerotic cardiovascular disease. The previous study have certified that IR could increase erythropoiesis, ensuing HCT/Hb and consequently increase blood viscosity [15]. In our study, serum UA levels were positively associated with RBC, Hb and HCT in males. Higher HCT was linked to an increased risk of hyperuricemia, which has demonstrated in a recent prospective study [16]. A study showed that mean arterial blood pressure was positively associated with RBC count, Hb and HCT. Average arterial blood pressure was higher in males than in females and this was related to higher values of RBC count, Hb and HCT in males as compared to females [17]. In addition, a cross-sectional survey in Japan observed an independent positive relationship between Hb and increased arterial stiffness only in individuals with BMI <25 kg/m^2. The multivariable adjusted odds ratios (OR) of 1-standard deviation increment in Hb for increased arterial stiffness were 1.40 in males and 1.19 in females [18]. A study showd that HCT was associated with prehypertension (systolic blood pressure: 120 mmHg-139 mmHg or diastolic blood pressure: 80 mmHg-89 mmHg) in people less than 60 years old [19]. A prospective study demonstrated that higher HCT, even within the normal range, was independently related to the incidence of hypertension in men [20]. Another prospective study found that HCT was independent predictors of type 2 diabetes mellitus in a graded fashion [21].

Platelet plays an important role in the formation of atherosclerotic plaque. Increased MPV was associated with shorter bleeding time and higher plasma thromboxane B2 levels, so MPV is a marker of PLT activation. A rat experiment found that serum UA inhibited Nitric Oxide (NO) production and consequently induced endothelial dysfunction [22]. IR related to reduction of NO synthesis was involved in the effect of UA on endothelial injury [23]. Local activation of oxidative stress and the renin-angiotensin system also mediated UA-induced endothelial dysfunction [24]. Cytokines released by dysfunctional endothelium might stimulate the bone marrow to produce large PLT. Besides, IR, oxidative stress and lower NO levels also directly influenced MPV [25,26]. A *vitro* study showed that urate crystals could induce platelet activation [27]. Our study showed a positive correlation of UA and MPV in females and postmenopausal females. Even the potential covariates of E2 was adjusted, this association remained. So we suggested that the gender-related difference in the association of serum UA with MPV might be caused by other factors but not estrogen levels. Recent studies have shown that MPV is an effective predictor and prognostic marker for cardiovascular disease. In patients with metabolic syndrome, CAD and stroke, levels of MPV increased [13]. A retrospective cohort study indicated that elevated MPV is associated with increased incidence of hypertension [28]. In addition, MPV can predict the risk of Acute Myocardial Infarction (AMI) and restenosis after coronary angioplasty [13]. A retrospective study included 553 patients with CKD, suggesting that MPV was negatively correlated with eGFR and significantly increased with progression of CKD [29]. A Chinese prospective stud showed that increased MPV was associated with all-cause mortality in patients with STEMI. MPV might be useful as a marker for risk stratification in Chinese patients with STEMI [30].

The present study possesses several noteworthy strengths. Firstly, we systematically and comprehensively explored the relationship between serum UA and hematological parameters in a healthy population, in order to rule out the influences of diseases. Secondly, we established rigorous exclusion criteria and made careful adjustments for potential confounding factors. Last and most importantly, we set up a female subgroup and adjusted for estrogen levels. The result demonstrated that gender-related difference in the association of serum UA with MPV may not be related to estrogen levels.

However, limitations should also be noticed. Firstly, this was a cross-sectional study, so we could not ascertain whether the relationship between serum UA and hematological parameters was an occasional phenomenon. Secondly, in our study, participants who underwent routine health check-up might not represent the general public, possibly leading to a selection bias. Lastly, because we did not get the information about smoking, alcohol and exercise habits, we could not adjust for these factors in multiple linear regression analysis.

Conclusion

The present study revealed the relationship of serum UA with hematological parameters in healthy Chinese adults and gender differences. The results indicated that serum UA was positively associated with RBC count, Hb and HCT in Chinese male adults, and was positively associated with MPV in Chinese female adults and postmenopausal females. Gender differences in the association between serum UA levels and MPV may not be related to estrogen levels. RBC count, Hb, HCT and MPV might assess the risk of hyperuricemia and guide stratified treatment. More work is needed to determine the cause-effect relationships between serum UA and hematological parameters.

Acknowledgement

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Disclosure Statement

All authors declare no conflicts of interest.

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