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Original Article

Association between the red cell distribution width and hyperuricaemia among 125134 adults aged from 18 to 94 years: a cross-sectional study

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Abstract: Objectives: To evaluate the association between red cell distribution width (RDW) and the prevalence of hyperuricaemia (HU). Methods: A total of 125134 subjects (68540 men and 56594 women) were included in this study. The unadjusted association between RDW and HU was assessed by the Chi-square trend test. A multi-variable logistic analysis model was applied to test the proposed association. Results: The prevalence of HU in the total subjects was 15.4% (22.2% for male, 6.6% for female). The Chi-square trend test suggested a significant association between elevated RDW and the prevalence of HU ($P < 0.01$) in the male population, but not in the female. The multivariable-adjusted model indicated that the prevalence of HU increased by 22% in the male subjects with the RDW ranged from 15.6%-41.4% (95th-97.5th percentile interval) and increased by 12% in the male subjects with the RDW > 41.4% (higher than 97.5th percentiles), when compared with the male subjects with the RDW < 15.7% (lower than 95th percentiles); P for trend was 0.02. For the female subjects, both the unadjusted result ($P = 0.74$) and the multivariable logistic regression showed that there was no significant association between elevated RDW and the prevalence of HU. Sensitivity analysis was conducted after excluding abnormal serum creatinine or limiting middle aged and old subjects, the results were similar for males and females. Conclusion: Elevated RDW was associated with HU in the male population, but not in the female. Males with the RDW higher than the normal range may be subjects with a higher risk of HU.

Keywords: Red cell distribution width, hyperuricaemia, cross-sectional study

Introduction

Hyperuricaemia (HU) is a major cause of disability, which receives increasing attention in recent decades because of its high prevalence worldwide [1-5]. Emerging data indicated that HU can increase the risk of a variety of diseases, such as gouty arthritis, renal calculi, hypertension, diabetes, cardiovascular disease, chronic kidney disease, etc. [6-10]. However, the specific pathogenesis of HU has not yet been fully elucidated. Meanwhile, early intervention for HU may have important public health and clinical implications.

The red cell distribution width (RDW), an index of the routine blood cell count, is regarded not only as a useful index for differential diagnosis in anaemia, but also as an emerging biomarker for predicting the early-stage renal functional damage in hypertension [11]; and the mortality in many cardiovascular diseases [12-14]. Although the specific biological mechanism of the elevated RDW is still unclear, inflammation and oxidative stress are speculated to play a great role [12]. HU was deemed to be associated with the inflammation status [15], and may contribute to cardiovascular events through the induction of endothelial dysfunction and the oxidative stress caused by xanthine oxidase activation [16]. Thus, elevated RDW and HU may share some common mechanisms.

Some previous studies suggested that increased RDW was associated with a high uric acid level in serum in a variety of settings, such

Table 1. Basic characteristics of male population according to categories of RDW

Parameters	Categories of RDW		
	< 95th percentiles (n = 65213)	95th-97.5th percentiles (n = 1617)	> 97.5th percentiles (n = 1710)
Median of RDW (%)	12.6	17.5	44.5
Age (years)	42.4 ± 13.4	43.9 ± 14.3	45.2 ± 13.6
BMI (kg/m^2)	24.5 ± 3.7	24.2 ± 3.5	24.4 ± 3.3
Hyperuricaemia (%)	22.6	26.2	24.7
Hb (g/L)	150.1 ± 11.2	136.6 ± 19.5	145.9 ± 11.8
FBS (mmol/L)	5.3 ± 1.4	5.3 ± 1.4	5.3 ± 1.1
SBP (mmHg)	123.5 ± 16.3	125.8 ± 17.6	128.2 ± 17.4
DBP (mmHg)	79.0 ± 11.8	79.1 ± 12.5	78.5 ± 12.0
ALT (U/L)	32.6 ± 32.3	32.1 ± 34.5	32.0 ± 33.8
Scr (μmol/L)	88.6 ± 23.5	90.9 ± 31.4	94.0 ± 19.5
TC (mmol/L)	4.8 ± 1.0	4.6 ± 1.1	4.7 ± 1.1
HDL-cholesterol (mmol/L)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3
LDL-cholesterol (mmol/L)	2.7 ± 0.9	2.5 ± 0.9	2.5 ± 0.8
TG (mmol/L)	1.8 ± 1.7	1.9 ± 2.0	2.1 ± 2.0

BMI: Body mass index, RDW: Red cell distribution width, Hb: Hemoglobin, FBS: Fasting blood glucose, SBP: Systolic blood pressure, DBP: Diastolic pressure, ALT: Alanine aminotransferase, Scr: Serum creatinine, TC: Total cholesterol, HDL: High density lipoprotein cholesterol, LDL-cholesterol: Low density lipoprotein cholesterol, TG: Triglyceride.

as hypertension [17, 18], chronic heart failure [19] and slow coronary flow [20]. However, to our best knowledge, there was not yet a study that examined the association between RDW and the prevalence of HU in the general population. The purpose of this study was to evaluate the association between RDW and the prevalence of HU based on the following hypothesis: elevated RDW is associated with HU, and RDW is a potential predictor of HU in the general population.

Materials and methods

Study population

This cross-sectional study was conducted in the Department of Health Examination Center Xiangya Hospital, Central South University in Changsha, Hunan Province, China. We obtained approval for this study from the ethics committee of Xiangya Hospital, Central South University. Also, we obtained written informed consent from the participants in our study. The study design has been published in our previous study which indicated that higher hematocrit was independently associated with the incidence of HU [21]. Routine health checkups are very common in China, because the Chinese government encourage people to take periodic medical examinations. Consecutive subjects who were undergone their first regular health examination between January 2007 and November 2014 were considered for inclusion in the present study. Firstly, 174648 subjects had data of uric acid (UA) and RDW, and 172067 of them aged 18 or over. Then, 144638 subjects were recorded for body mass index (BMI). After excluding subjects with missing data on total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglyceride (TG), blood glucose, blood pressure, hemoglobin (Hb), serum creatinine (SCr) and alanine aminotransferase (ALT), 125134 subjects were included in the present study.

Exposure assessment

All blood samples were drawn after a 12-hour overnight fast and were kept at 4°C until analysis. RDW was measured by the electrical impedance method, and Hb was measured by the spectrophotometric method. The blood samples were analyzed on the Beckman Coulter LH750 automated hematology analyzer (Beckman Coulter Inc., Miami, FL, USA). Other biochemical values including UA, blood glucose, blood lipid (TC, LDL, HDL, TG), SCr and ALT were detected by the Beckman Coulter AU 5800 (Beckman Coulter Inc., Brea, CA, USA). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an electronic sphygmomanometer. BMI was calculated as weight (kg) divided by height squared (m^2).

HU was defined as UA ≥ 416 μmol/L for male population and ≥ 360 μmol/L for female population. Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Anemia was defined as Hb < 120 g/L for male population and < 110 g/L for female population. Hyperlipemia was defined as TC ≥ 6.22

Table 2. Basic characteristics of female population according to categories of RDW

Parameters	Categories of RDW		
	< 95th percentiles (n = 53816)	95th-97.5th percentiles (n = 1364)	> 97.5th percentiles (n = 1414)
Median of RDW (%)	12.6	17.7	43.6
Age (years)	42.3 ± 13.5	41.6 ± 10.6	42.8 ± 13.2
BMI (kg/m^2)	22.4 ± 3.2	22.8 ± 3.2	22.4 ± 0.3
Hyperuricaemia (%)	6.6	4.6	7.3
Hb (g/L)	128.2 ± 10.1	104.7 ± 17.7	123.8 ± 10.4
FBS (mmol/L)	5.2 ± 1.0	5.1 ± 1.0	5.1 ± 0.7
SBP (mmHg)	117.0 ± 18.0	118.4 ± 18.4	118.8 ± 19.3
DBP (mmHg)	73.0 ± 11.2	73.4 ± 11.4	72.1 ±11.5
ALT (U/L)	19.8 ± 19.3	19.8 ± 63.6	20.6 ±41.2
Scr (μmol/L)	65.1 ± 18.4	64.2 ± 16.3	71.7 ± 39.0
TC (mmol/L)	4.7 ± 1.0	4.4 ± 0.9	4.5 ± 0.9
HDL-cholesterol (mmol/L)	1.6 ± 0.4	1.5 ±0.4	1.5 ± 0.3
LDL-cholesterol (mmol/L)	2.6 ± 0.8	2.4 ± 0.8	2.5 ± 0.7

RDW: Red cell distribution width, BMI: Body mass index, Hb: Hemoglobin, FBS: Fasting blood glucose, SBP: Systolic blood pressure DBP: Diastolic pressure, ALT: Alanine aminotransferase, Scr: Serum creatinine, TC: Total cholesterol, HDL: High density lipoprotein cholesterol, LDL-cholesterol: Low density lipoprotein cholesterol, TG: Triglyceride.

mmol/L or LDL ≥ 4.14 mmol/L or TG ≥ 2.26 mmol/L.

Statistical analysis

The quantitative data are expressed as mean ± standard deviation, and the qualitative data are expressed in percentage. According to a previous study [22], the RDW was classified into three categories in men and women population based on the following distribution: < 95th percentile (< 15.6% in men, < 16.1% in women), 95th-97.5th percentile (15.6%-41.4% in men, 16.1%-38.7% in women) and > 97.5th percentile (> 41.4% in men, > 38.7% in women). Unadjusted association between RDW and HU was assessed by Chi-square trend test. In order to calculate the adjusted association between RDW and the prevalence of HU, a multi-variable model were adopted in the logistic regression analyses: the multi-variable model includes age, BMI (≥ 25 kg/m^2, < 25 kg/m^2), diabetes, hypertension, anemia, ALT (> 40 U/L, ≤ 40 U/L), SCr (≥ 132.6 μmol/L, < 132.6 μmol/L) and hyperlipemia. Tests for linear trends were conducted based on logistic regression using a median variable of RDW level in each category. Sensitivity analysis was conducted by running the same logistic regression after excluding subjects younger than 40 or with abnormal SCr (≥ 132.6 μmol/L). All data analyses were performed using SPSS 17.0; a *P* value less than 0.05 was considered to be statistically significant.

Results

A total of 125134 subjects (68540 men and 56594 women), aged from 18 to 94 years (mean 42.4), were included in the present cross-sectional study. The prevalence of HU in the total subjects was 15.4% (22.2% for male, 6.6% for female), which was similar to the prevalence reported by other studies conducted for the Chinese population [3, 4]. The basic characteristics of male and female population were separately illustrated in **Tables 1** and **2**.

The outcomes with respect to the association between elevated RDW and HU in the male population were listed in **Table 3**. The Chi-square trend test suggested a significant association between elevated RDW and the prevalence of HU (P = 0.00) in males. After adjusting the factors of age, BMI, diabetes, hypertension, anemia, ALT, SCr and hyperlipemia, the significant association was still valid. The multivariable adjusted ORs (95% CI) of the prevalence of HU were 1.22 (1.09, 1.38) in 95th-97.5th percentile interval and 1.12 (1.00, 1.26) in higher than 97.5th percentiles range of RDW comparing to normal RDW (P for trend = 0.02). Compared with the male subjects with the RDW < 15.6%, the prevalence of HU of the male subjects with the RDW ranged from 15.6%-41.4% and with the RDW > 41.4% was increased by 22% and 12% respectively. Sensitivity analysis was conducted after excluding abnormal serum creatinine (Scr) (≥ 132.6 μmol/L), and the results were similar. The multivariable adjusted ORs (95% CI) of the prevalence of HU were 1.23 (1.09, 1.38) in 95th-97.5th percentile interval and 1.14 (1.01, 1.27) in higher than 97.5th percentiles range of RDW comparing to normal RDW (P for trend = 0.01). Sensitivity analysis was also conducted for the

Table 3. Association between RDW and hyperuricaemia in male population

Parameters	Categories of RDW			P for trend
	< 95th percentiles (n = 65213)	95th-97.5th percentiles (n = 1617)	> 97.5th percentiles (n = 1710)	
Hyperuricaemia (%)	22.6	26.2	24.7	0.00#
Multivariable adjusted OR (95% CI)	Reference	1.22 (1.09, 1.38)	1.12 (1.00, 1.26)	0.02

#Unadjusted P for trend. RDW: Red cell distribution width, OR: Odds ratio, 95% CI: 95% confidence interval. Multivariable included: age, BMI (≥ 25 kg/m^2, < 25 kg/m^2), diabetes, hypertension, anemia, ALT (> 40 U/L, ≤ 40 U/L), SCr (≥ 132.6 μmol/L, < 132.6 μmol/L) and hyperlipemia.

Table 4. Association between RDW and hyperuricaemia in female population

Parameters	Categories of RDW			P for trend
	< 95th percentiles (n = 53816)	95th-97.5th percentiles (n = 1364)	> 97.5th percentiles (n = 1414)	
Hyperuricaemia (%)	6.6	4.6	7.3	0.74#
Multivariable adjusted OR (95% CI)	Reference	0.79 (0.60, 1.05)	1.09 (0.89, 1.35)	0.52

#Unadjusted P for trend. RDW: Red cell distribution width, OR: Odds ratio, 95% CI: 95% confidence interval. Multivariable included: age, BMI (≥ 25 kg/m^2, < 25 kg/m^2), diabetes, hypertension, anemia, ALT (> 40 U/L, ≤ 40 U/L), SCr (≥ 132.6 μmol/L, < 132.6 μmol/L) and hyperlipemia.

middle aged and old subjects (equal to or above 40 years old), and the results remained unchanged. The multivariable adjusted ORs (95% CI) of the prevalence of HU were 1.24 (1.06, 1.46) in 95th-97.5th percentile interval and 1.21 (1.04, 1.40) in higher than 97.5th percentiles range of RDW comparing to normal RDW (P for trend = 0.01).

The outcomes with respect to the association between RDW and HU in female subjects were listed in **Table 4**. Both the unadjusted association (P = 0.74) and the multivariable logistic regression showed that there was no significant relationship between elevated RDW and the prevalence of HU in females. The multivariable adjusted ORs (95% CI) of the prevalence of HU were 0.79 (0.60, 1.05) in 95th-97.5th percentile interval and 1.09 (0.89, 1.35) in higher than 97.5th percentiles range of RDW comparing to normal RDW (P for trend = 0.52). Sensitivity analysis was conducted after excluding abnormal Scr or limiting middle aged and old subjects. There was still no significant association observed between elevated RDW and the prevalence of HU in females.

Discussion

This is the first study that demonstrated a significantly positive association between elevated RDW and HU in the male population, but such association was not observed in females. Elevated RDW (higher than the normal range) was found to be an independent influencing factor for HU in the male population.

Some previous studies have shown that RDW was correlated with the serum uric acid in a variety of settings [3, 4]. Recently, Luo M et al. indicated that RDW might be independently associated with serum uric acid in patients with newly diagnosed hypertension, and patients with high uric acid had a higher RDW [17]. Tosu AR et al. suggested that RDW and uric acid level were significantly higher in non-dipper hypertension patients when compared with dipper hypertension patients and controls [18]. Kaya A et al. also observed that RDW and uric acid increased simultaneously in patients with stable chronic heart failure [19]. Similarly, Kalay N et al. reported that patients with slow coronary flow exhibited a significantly higher RDW and serum uric acid level [20]. When compared with healthy controls, prehypertensive and hypertensive patients had a higher RDW and a slightly higher serum uric acid (approaching significant) [23]. The present study also found a significant association between elevated RDW and HU in the male population. Considering the various negative impacts of HU on human body [6-10], especially on the male population (with a higher incidence) [1, 3, 5], early management of HU should be considered. This study suggested that males with the RDW higher than the normal range may be subject to a higher risk of HU.

A number of epidemiological studies showed that RDW was significantly associated with the C-reactive protein (CRP) status [24-27], which is the most sensitive biomarker for inflammation. In addition, emerging data also revealed that serum uric acid was positively associated with the CRP levels [28-36]. On the other hand, both RDW and HU were found to be correlated with oxidative stress [12, 16]. In view of the above findings, RDW and uric acid may increase concurrently in some specific disease states, and share some common mechanisms such as inflammation and oxidative stress. The results of this study provided an in-depth insight into the pathogenesis of HU. Subsequent researches may focus on clarifying the mechanism of the correlation between elevated RDW and HU.

The present study has several strengths. Firstly, this is the first study conducted on a large population-based sample (125134 participants) that directly correlated elevated RDW with HU. Secondly, this is also the first study showing that elevated RDW was associated with HU in the male population. Thirdly, the result of the univariate analysis was consistent with the result of the multivariable model adjusted by age, BMI, diabetes, hypertension, anemia, ALT, SCr and hyperlipemia, which greatly improved the reliability of the findings.

Limitations of the present study should also be admitted. The cross-sectional design of this study precluded causal correlations, and thus, further prospective cohort studies should be conducted to establish a causal relationship between RDW and HU. Since no previous study examined the association between RDW and HU, the value of this study should not be blotted due to the cross-sectional nature. In addition, since RDW is an inexpensive and routine index, the results of this study may contribute to the early identification of HU for the male population. However, it is noteworthy that the conclusion of this study should be cautiously applied to other populations (non-Asian).

In conclusion, the present study showed that elevated RDW was associated with HU in the male population, but not in the female. Males with the RDW higher than the normal range may be subjects with a higher risk of HU.

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Disclosure of conflict of interest

None.

Authors' contribution

GHL and TY conceived and designed the study. CZ, JW, DXX, SGG, YSL, LJL and XX performed data collection. JW and TBY conducted the data analysis. GHL, TY and CZ drafted the initial manuscript and all authors participated in reviewing the draft assisting with revisions. All authors approved the final version of the manuscript.

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