Original Article

Associations of Peripheral Total and Differential Leukocyte Count with Features of Hyperuricemia in Chinese Male Steel Workers

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Objective: There is increasing evidence that leukocytes play a central role in obesity, glucose intolerance, type 2 diabetes mellitus, and cardiovascular diseases, but the significance of differential leukocyte count in hyperuricemia is largely unknown. The aims of this study were to examine the relationship between the features of hyperuricemia and peripheral leukocyte counts and to explore whether leukocyte counts are associated with hyperuricemia.

Methods: We enrolled 3,174 male steel workers who responded to a cross-sectional survey on basic demographic characteristics, life-style, and sleep. All workers in the plant received a periodic health checkup, and peripheral leukocyte counts were recorded.

Results: The workers with hyperuricemia had higher white blood cell (WBC) (6.483 ± 1.623 vs. 6.200 ± 1.604, $p < 0.0001$), neutrophil (3787 ± 1242 vs. 3658 ± 1230, $p = 0.005$), monocyte (363 ± 115 vs. 345 ± 119, $p < 0.0001$), and lymphocyte (2125 ± 605 vs. 1995 ± 572, $p < 0.0001$) counts than those without hyperuricemia. Using stepwise linear regression analysis, peripheral total WBC, monocyte, neutrophil, and lymphocyte counts were independently and significantly associated with hyperuricemia. In addition, when the subjects were divided into quartiles according to serum uric acid concentration, we found significant positive associations of serum uric acid level with total WBC count (6.166 ± 1.681, 6.151 ± 1.526, 6.371 ± 1.580, and 6.555 ± 1.637 × 10^9/L, Q1 – Q4, respectively, $p < 0.0001$), neutrophil count (3669 ± 1323, 3587 ± 1134, 3765 ± 1196, and 3810 ± 1263 × 10^9/L, Q1 – Q4, respectively, $p = 0.002$), monocyte count (343 ± 119, 343 ± 116, 356 ± 120, and 368 ± 115 × 10^9/L, Q1 – Q4, respectively, $p < 0.0001$), and lymphocyte count (1958 ± 555, 2015 ± 584, 2050 ± 581, and 2163 ± 617 × 10^9/L, Q1 – Q4, respectively, $p < 0.0001$).

Conclusions: Our results indicate that total and differential leukocyte counts were positively associated with hyperuricemia, suggesting their importance as biological markers of hyperuricemia in Chinese male steel workers.

Key words: hyperuricemia, lymphocyte, monocytes, neutrophil, steel workers

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Introduction

Hyperuricemia is very common, with a prevalence of up to 15% − 20% reported in population-based studies.[1] In addition, hyperuricemia often accompanies metabolic syndrome, hypertension, diabetes, dyslipidemia, chronic renal disease (CKD), and obesity. Serum uric acid level is known to vary significantly depending on meals, lifestyle, gender, and previous use of diuretics.[2] The prevalence and incidence of hyperuricemia have steadily increased worldwide over the past 40 years. Taiwan has a relatively high rate of hyperuricemia, with a prevalence of 43.7% in men and 27.4% in women aged ≥ 15 years.[3] The high prevalence of hyperuricemia suggests that hyperuricemia may be an important risk factor for cardiovascular disease (CVD) in Taiwan. Tomita et al. has reported that hyperuricemia is strongly associated with the relative risks of all-cause mortality, coronary heart disease, stroke, hepatic disease and renal failure, and suggested that serum uric acid may be an important risk factor for reduced life expectancy.[4] Hyperuricemia is also implicated in the pathogenesis of several disease conditions, including platelet dysfunction, coagulation disorders, endothelial dysfunction, inflammation, and atrial fibrillation.

Peripheral white blood cell (WBC) count has been shown to be associated with coronary artery disease (CAD),[5] insulin resistance, type 2 diabetes,[6] stroke,[7] diabetic micro- and macrovascular complications,[8] and metabolic syndrome.[9] An association between leukocyte counts and CAD, which has been observed in prospective and retrospective cohort studies as well as in case-control studies, persists after adjusting for multiple coronary heart disease (CHD) risk factors (e.g., smoking).[10] In addition, previous study also demonstrated an association between hematological indicators and hyperuricemia.[11] Peripheral blood leukocytes are composed of polymorphonuclear and mononuclear leukocytes, including neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Polymorpho- and mononuclear leukocytes have been reported to be activated by advanced glycation end products,[12] angiotensin II,[13] cytokines,[14] and oxidative stress,[15] in a state of hyperglycemia. Leukocytes may be activated through the release of superoxide[16] and cytokines such as tumor necrosis factor-α (TNF-α),[17] interleukin-1β, transforming growth factor β1,[18] nuclear factor-κB (NF-κB),[19] monocyte chemoattractant protein 1, and other mediators[17] that contribute to the pathogenesis of diabetic micro- and macrovascular complications. Elevated differential cell counts, including those of neutrophils, monocytes, and eosinophils also predict the future incidence of CAD.[53] However, there is no research addressing the significance of differential leukocyte count in hyperuricemia.

Among the many pollutants produced in different industrial processes that iron and steel workers are exposed to, lead is one of the most notorious health hazards. Previous studies have identified risk factors for elevated blood lead levels in iron and steel workers.[20,21] An increased serum uric acid level is a predictor of the development of gout in the general population.[22] Chronic occupational exposure to lead may also cause hyperuricemia and gout due to the inhibition of urate excretion.[22,23] Furthermore, previous studies demonstrated significant associations of shift work with hyperuricemia, overweight, obesity, and increased total cholesterol level among male steel workers.[24-26] Moreover, our recent study also found that peripheral total and differential leukocyte counts are significantly higher in Chinese steel shift workers.[27] The aims of the present study, therefore, were to examine the relationship between the features of hyperuricemia and peripheral leukocyte counts as well as to explore whether leukocyte counts are associated with hyperuricemia in Chinese male steel workers.

Materials and Methods

Study population

This study was conducted at a university hospital from March to June 2010, and enrolled 3,376 male workers aged 26 – 67 years from a steel company in southern Taiwan. Two hundred and two workers were excluded due to a history of infectious diseases within the past 3 months, kidney disease, liver disease, cardiovascular disease, thyroid disease, autoimmune disease, or cancer. Those with missing data were also excluded. The remaining 3,174 patients were analyzed. All of the workers at the steel company underwent a legally required health examination once a year. This study was approved by the Human Research Ethics Committee of E-Da Hospital and I-Shou University (EDAH IRB No. EMRP-104-089). Written informed consents were obtained from all participants.

Questionnaire surveys

Medical histories were investigated through the use of a self-administered questionnaire during annual health examination. Information on basic demographic characteristics and lifestyle, including sex, age, sleep quality, job type, health condition, physical exercise, smoking habit, and alcohol consumption, were also obtained from the questionnaire. All data were confirmed in individual interviews conducted by occupational health physicians. The degree of physical exercise was assessed by the question "How often did you exercise during the past month?" The response options included " hardly ever", "once", and "twice or more". For work schedule, the participants were asked whether they were daytime workers (8:00 – 17:00) or shift workers working rotating shifts comprising morning (7:00 – 15:00), afternoon (15:00 – 23:00), and night (23:00 – 7:00) shifts. Sleep quality was assessed by the question "How often did you have poor sleep during the past month?" The response options were "almost never", "sometimes", and "often or almost always".

Diagnosis

The onset of hyperuricemia was determined for each worker according to the results of the annual health examination and medical histories through individual interviews. Based on previous studies, we defined hyperuricemia as a serum uric acid level ≥ 7.0 mg/dL,[28-30] as measured by the uricase method. This represents the solubility limit of urate in serum at 37°C. Uric acid levels above 7.0 mg/dL result in supersaturated solutions that are prone to crystal formation.[31] Arterial hypertension was diagnosed in subjects with resting blood pressure ≥ 140/90 mmHg, and in subjects with a history of hypertension and in those taking anti-hypertensives. Hyperlipidemia was defined as a triglyceride level ≥ 150 mg/dL, and/or a HDL-cholesterol level of < 40 mg/dL for men and < 50 mg/dL for women, and/or a total cholesterol level of ≥ 200 mg/dL, and/or a LDL-cholesterol level of ≥ 100 mg/dL, or those undergoing treatment for lipid disorders according to the Adult Treatment Panel (ATP) III criteria.[32] The diagnosis of diabetes mellitus (DM) was made based on the definition of a glycated hemoglobin (HbA1c) level of ≥ 6.5% (48 mmol/mol) or previous criteria of an elevated fasting glucose (≥ 126 mg/dL [7.0 mmol/L]) or two-hour glucose (≥ 200 mg/dL [11.1 mmol/L]) concentration according to the 2016 American Diabetes Association (ADA) guideline,[33] or a history of treatment for DM. For kidney function, the estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease - Epidemiological Collaboration (CKD-EPI) two-concentration race equation.[34] The patients were stratified by eGFR into CKD stage 1 (≥ 90 mL/min/1.73 m^2), stage 2 (60-89 mL/min/1.73 m^2), stage 3 (30-59 mL/min/1.73 m^2), and stage 4 (≤ 29 mL/min/1.73 m^2) according to the Kidney Disease

Outcomes Quality Initiative (KDOQI) clinical practice guidelines of the National Kidney Foundation. Smoking status was classified as never having smoked, former smoker (quit smoking for at least 1 year), or current smoker. Drinking status was classified as never, daily, or occasionally. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Based on the definition from the Bureau of Health Promotion, Department of Health, Taiwan, the respondents were categorized as being underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5 − 23.9 kg/m^2), overweight (BMI 24.0 − 26.9 kg/m^2), or obese (BMI ≥ 27.0 kg/m^2).

Measures

Peripheral blood samples were taken from the antecubital vein of the workers after fasting for at least 8 hours. Complete blood cell counts and serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), glucose, HbA1c, uric acid, lipid profiles (including plasma triglycerides, total cholesterol, LDL-C, HDL-C), and serum creatinine were also measured during health checkups and determined in all workers using standard commercial methods with a parallel, multichannel analyzer (Hitachi 7170A) as described in our previous report.[23] Peripheral leukocyte analysis included total leukocyte count and differential percentages of monocytes, neutrophils, lymphocytes, eosinophils, and basophils using an automated cell counter (XE-2100 Hematology Alpha Transportation System, Sysmex Corporation, Kobe, Japan). The absolute count of a leukocyte subtype was calculated as the product of its respective differential percentage and total leukocyte count. In addition, serum C-reactive protein (CRP) was measured using a high sensitivity method (IMMAGE; Beckman Coulter, Immunochemistry Systems, Brea, CA) that had a detection limit of 0.2 mg/L. The intra-assay coefficients of variation were 4.2% − 8.7% for high-sensitivity (hs)-CRP.

Statistical analysis

Descriptive data were examined for all variables. Continuous, normally distributed variables are expressed as mean ± SD, and non-normally distributed variables as the median (interquartile range). The Kolmogorov-Smirnov test was used to evaluate the normality of distribution. Statistical differences in variables between groups were tested using the Student's t test. Categorical data are expressed as a number (percentage), and intergroup comparisons were performed using the χ^2 test. Mean values were compared by ANOVA among different groups. Because the distributions of serum triglyceride, SGOT, SGPT, hs-CRP, and WBC count were skewed, logarithmically transformed values were used for statistical analysis. Simple and multiple linear stepwise regression analyses were used to examine the associations and independence of peripheral total and differential leukocyte counts with the values of other parameters. All statistical analyses were performed using SAS software, v10.0 (SAS Institute, Cary, NC). All of the statistical analyses were two-sided, and a p value < 0.05 was considered to be significant.

Results

A total of 3,174 male workers (age, 43 ± 7 years old) were included in this study, and their clinical characteristics are shown in Table 1. The total prevalence of hyperuricemia was 36.9%. The workers with hyperuricemia had higher rates of occasional drinking (57.5% vs. 52.6%), obesity (34.2% vs. 18.5%), hyperlipidemia (58.9% vs. 44.3%), and stage 3 CKD (5.8% vs. 1.8%) as well as lower rates of never drinking (41.4% vs. 46.8%) and stage 1 CKD (8.7% vs. 14.2%) than those without hyperuricemia. In addition, the workers with hyperuricemia were younger, and had a higher BMI, waist circumference, systolic blood pres-

Table 1. Clinical characteristics of the study subjects

Variable	Hyperuricemia†	Normal uricemia	*p*-value
No	1172	2002	
Smoking			
Never	620 (52.9)	1027 (51.3)	0.421
Former	135 (11.5)	198 (9.9)	0.142
Current	417 (35.6)	777 (38.8)	0.079
Drinking			
Never	485 (41.4)	937 (46.8)	0.005
Daily	13 (1.1)	13 (0.7)	0.191
Occasionally	674 (57.5)	1052 (52.6)	0.011
Physical exercise			
Hardly ever	198 (16.9)	347 (17.3)	0.783
Once	109 (9.3)	167 (8.3)	0.378
Twice or more	865 (73.8)	1488 (74.3)	0.741
Poor sleep			
Almost never	895 (76.4)	1497 (74.8)	0.385
Sometimes	192 (16.4)	350 (17.5)	0.446
Often or almost always	85 (7.3)	155 (7.7)	0.739
Type of work			
Line work	757 (64.6)	1275 (63.7)	0.615
Office work	186 (15.9)	334 (16.7)	0.567
Engineering	151 (12.9)	245 (12.2)	0.558
Management	78 (6.7)	148 (7.4)	0.389
Shift work	534 (45.6)	862 (43.1)	0.198
Obesity	401 (34.2)	370 (18.5)	< 0.0001
Hypertension	99 (8.5)	141 (7.0)	0.157
Hyperlipidemia	690 (58.9)	886 (44.3)	< 0.0001
Diabetes mellitus	12 (1.0)	38 (1.9)	0.075
Chronic kidney disease			
Stage 1 (≥ 90)	102 (8.7)	285 (14.2)	< 0.0001
Stage 2 (60-89)	1000 (85.3)	1680 (83.9)	0.275
Stage 3 (30-59)	68 (5.8)	36 (1.8)	< 0.0001
Stage 4 (≤ 29)	2 (0.2)	4 (0.2)	0.855

Data expressed as n (%). *P*-value calculated by Chi-square test. †: Serum uric acid level ≥ 7.0 mg/dL.

sure (SBP) and diastolic blood pressure (DBP) compared to those without. The workers with hyperuricemia also had higher levels of total cholesterol, triglycerides, LDL-C, SGOT, SGPT, uric acid, creatinine, hs-CRP as well as elevated WBC, neutrophil, and monocyte, lymphocyte counts, but lower HbA1c, HDL-C concentrations and eGFR compared to those without (Table 2). There were no significant differences in fasting blood sugar level, eosinophil and basophil counts, smoking habit, daily drinking, physical exercise, poor sleep, type of work, shift work, hypertension, diabetes mellitus, and stages 2 and 4 CKD between the two groups.

Univariate analysis revealed that the total WBC count was associated negatively with age, and positively with smoking, hypertension, hyperlipidemia, obesity, and hyperuricemia, while the monocyte count was associated negatively with age, and positively with alcohol consumption, smoking, hyperlipidemia, obesity, and hyperuricemia. The neutrophil count was associated positively with smoking, hypertension, obesity, and hyperuricemia, whereas the lymphocyte count was associated negatively with age, and positively with smoking, hyperlipidemia, obesity, and hyperuricemia (all $p < 0.05$; Table 3). Furthermore, multiple linear stepwise regression analysis was conducted for all of these items. Significantly independent factors for the total WBC count were shown to be age ($p = 0.001$), alcohol consumption ($p = 0.049$), smoking habit ($p < 0.0001$), hyperlipidemia ($p = 0.004$), obesity ($p < 0.0001$), and hyperuricemia ($p = 0.002$). For the monocyte count, those were shown to be age ($p < 0.0001$), smoking habit ($p < 0.0001$), obesity ($p < 0.0001$), and hyperuricemia ($p = 0.001$). For the neutrophil count, those were shown to be smoking habit ($p < 0.0001$), obesity ($p < 0.0001$), and hyperuricemia ($p = 0.028$). For the lymphocyte count, those were shown to be age ($p < 0.0001$), smoking habit (p < 0.0001), hyperlipidemia ($p < 0.0001$), obesity ($p < 0.0001$), and hyperuricemia ($p = 0.002$) (Table 4).

When the subjects were divided into quartiles according to serum uric acid, we found that the values of age, uric acid, fasting blood sugar, total cholesterol, triglyceride, HDL-C, LDL-C, and creatinine levels differed among the four levels of uric acid and the total WBC count (6.166 ± 1.681, 6.151 ± 1.526, 6.371 ±

1.580, and 6.555 ± 1.637x10^9/L, Q1 – Q4, $p < 0.0001$), neutrophil count (3669 ± 1323, 3587 ± 1134, 3765 ± 1196, and 3810 ± 1263 10^9/L, Q1 – Q4, $p = 0.002$), monocyte count (343 ± 119, 343 ± 116, 356 ± 120, and 368 ± 115 10^9/L, Q1 – Q4, $p < 0.0001$), and lymphocyte count (1958 ± 555, 2015 ± 584, 2050 ± 581, and 2163 ± 617 10^9/L, Q1 – Q4, $p < 0.0001$) were prominently related to serum uric acid levels (Table 5). In addition, log serum hs-CRP concentrations were significantly positively associated with uric acid level (Fig. 1).

Table 2. Biochemical characteristics of the study subjects

Variable	Hyperuricemic†	Normouricemic	*p*-value
Number of subjects	1172	2002	
Age (years)	42.5 ± 7.1	43.1 ± 7.6	0.020
Body mass index (kg/m^2)	26.1 ± 3.6	24.3 ± 3.3	< 0.0001
Waist circumference (cm)	86.6 ± 8.8	82.4 ± 8.4	< 0.0001
Systolic BP (mmHg)	127 ± 16	122 ± 15	< 0.0001
Diastolic BP (mmHg)	81 ± 11	78 ± 10	< 0.0001
HbA1c (%)	5.6 ± 0.5	5.7 ± 0.8	0.047
Fasting sugar (mg/dL)	100.3 ± 14.6	101.5 ± 23.7	0.119
Total cholesterol (mg/dL)	198.9 ± 35.7	190.5 ± 32.8	< 0.0001
Triglyceride (mg/dL)	139.0 (97.0 − 204.0)	104.0 (73.0 − 155.0)	< 0.0001
HDL-cholesterol (mg/dL)	45.0 ± 9.3	47.4 ± 10.5	< 0.0001
LDL-cholesterol (mg/dL)	115.8 ± 31.2	110.5 ± 28.6	< 0.0001
SGOT (U/L)	29.0 (24.0 − 37.0)	26.0 (22.0 − 32.0)	< 0.0001
SGPT (U/L)	38.0 (27.0 − 56.0)	31.0 (22.0 − 43.0)	< 0.0001
Uric acid (mg/dL)	8.0 ± 0.9	5.8 ± 0.8	< 0.0001
Creatinine (mg/dL)	1.2 ± 0.3	1.2 ± 0.4	0.0001
eGFR (mL/min/1.73 m^2)	75.8 ± 11.0	79.3 ± 10.6	< 0.0001
Hs-CRP (mg/L)	1.0 (0.5 − 2.6)	0.7 (0.4 − 1.5)	0.028
White blood cell count (10^9/L)	6.275 (5.360 − 7.387)	5.970 (5.110 − 7.083)	< 0.0001
Neutrophil count (10^9/L)	3787 ± 1242	3658 ± 1230	0.005
Monocyte count (10^9/L)	363 ± 115	345 ± 119	< 0.0001
Lymphocyte count (10^9/L)	2125 ± 605	1995 ± 572	< 0.0001
Eosinophil count (10^9/L)	177 ± 125	172 ± 129	0.277
Basophil count (10^9/L)	30 ± 19	29 ± 18	0.440

Data are shown as means ± SD or medians (interquartile range). *P*-value calculated by Student's t test; BP: Blood pressure; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; Hs-CRP: High-sensitivity C-reactive protein; eGFR: Estimated glomerular filtration rates were calculated using the CKD-EPI two-level race equation.[30] †: Serum uric acid level ≥ 7.0 mg/dL.

Table 3. Association of covariates with peripheral total and differential leukocyte counts

	Total WBC count		Monocyte count		Neutrophil count		Lymphocyte count	
Factor	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
Age	-0.042	0.017	-0.058	0.001	-0.016	0.360	-0.066	< 0.0001
Alcohol use	0.016	0.398	0.037	0.049	0.001	0.940	0.025	0.182
Smoking	0.237	< 0.0001	0.253	< 0.0001	0.175	< 0.0001	0.200	< 0.0001
Hypertension	0.046	0.013	0.004	0.832	0.059	0.002	0.001	0.940
Diabete mellitus	0.031	0.111	0.018	0.363	0.038	0.052	0.002	0.908
Hyperlipidemia	0.088	< 0.0001	0.041	0.020	0.025	0.163	0.177	< 0.0001
Obesity	0.168	< 0.0001	0.119	< 0.0001	0.121	< 0.0001	0.169	< 0.0001
Hyperuricemia	0.085	< 0.0001	0.074	< 0.0001	0.050	0.005	0.106	< 0.0001

Table 4. Stepwise linear regression analysis of covariates associated with peripheral total and differential leukocyte counts

	Total WBC count			Monocyte count			Neutrophil count			Lymphocyte count		
Factor	β	95% CI	*p*-value	β	95% CI	*p*-value	β	95% CI	*p*-value	β	95% CI	*p*-value
Age	-0.064	-0.02 – -0.01	0.001	-0.073	-1.88 – -0.60	< 0.0001	NA		NA	-0.091	-0.07 – -0.04	< 0.0001
Alcohol use	-0.038	-0.25 – -0.00	0.049	NA		NA	NA		NA	NA		NA
Smoking	0.243	0.66 – 0.91	< 0.0001	0.253	1.46 – 9.40	< 0.0001	0.167	5.61 – 12.76	< 0.0001	0.200	5.71 – 10.32	< 0.0001
Hypertension	NA		NA	NA		NA	NA		NA	NA		NA
Diabetes mellitus	NA		NA	NA		NA	NA		NA	NA		NA
Hyperlipidemia	0.055	0.06 – 0.30	0.004	NA		NA	NA		NA	0.152	3.67 – 12.74	< 0.0001
Obesity	0.142	0.40 – 0.69	< 0.0001	0.088	3.86 – 5.24	< 0.0001	0.119	5.52 – 9.44	< 0.0001	0.125	8.84 – 14.77	< 0.0001
Hyperuricemia	0.059	0.07 – 0.33	0.002	0.062	5.99 – 14.78	0.001	0.058	5.18 – 8.23	0.028	0.061	8.09 – 10.40	0.002

NA: not applicable.

Table 5. Association of covariates with peripheral total and differential leukocyte counts

Parameter	1st quartile 1 − 5.7	2nd quartile 5.7 − 6.5	3rd quartile 6.5 − 7.4	4th quartile 7.4 − 12.8	*p*-value
Uric acid (mg/dL)	5.1 ± 0.6	6.2 ± 0.2	7.0 ± 0.3	8.4 ± 0.8	< 0.0001
Age (years)	43.8 ± 7.7	42.9 ± 7.7	42.3 ± 7.2	42.5 ± 7.1	0.0003
Fasting sugar (mg/dL)	103.2 ± 29.7	100.2 ± 17.0	99.8 ± 17.2	100.7 ± 14.4	0.004
Total cholesterol (mg/dL)	187.3 ± 31.8	192.6 ± 33.2	195.0 ± 34.0	200.4 ± 36.4	< 0.0001
Triglyceride (mg/dL)	94.0 (68.0 − 144.0)	110.0 (78.0 − 158.5)	124.0 (84.0 − 182.0)	144.0 (100.0 − 218.0)	< 0.0001
HDL-cholesterol (mg/dL)	48.5 ± 10.9	46.7 ± 10.3	46.0 ± 9.6	44.6 ± 9.1	< 0.0001
LDL-cholesterol (mg/dL)	107.5 ± 28.2	112.5 ± 28.4	113.5 ± 29.4	117.0 ± 32.0	< 0.0001
Creatinine (mg/dL)	1.1 ± 0.3	1.2 ± 0.1	1.2 ± 0.5	1.2 ± 0.3	< 0.0001
WBC count (10^9/L)	5.895 (5.005 − 7.010)	5.980 (5.110 − 7.050)	6.170 (5.280 − 7.223)	6.340 (5.400 − 7.480)	< 0.0001
Neutrophil count (10^9/L)	3669 ± 1323	3587 ± 1134	3765 ± 1196	3810 ± 1263	0.002
Monocyte count (10^9/L)	343 ± 119	343 ± 116	356 ± 120	368 ± 11	< 0.0001
Lymphocyte count (10^9/L)	1958 ± 555	2015 ± 584	2050 ± 581	2163 ± 617	< 0.0001

Continuous variables were given as mean ± SD or median (interquartile range). HDL, high-density lipoprotein; LDL, low- density lipoprotein; WBC, white blood cell.

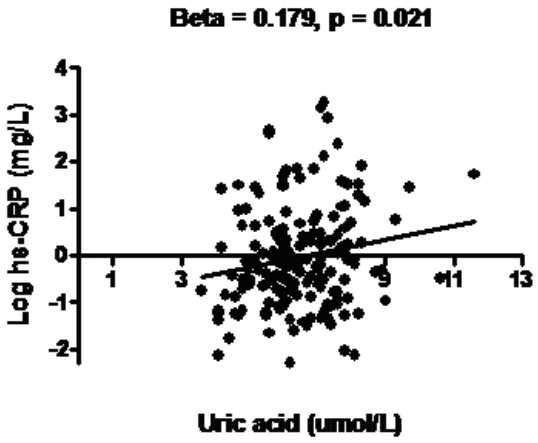

Fig. 1 Significant positive association between log serum high-sensitivity C-reactive protein concentrations and uric acid levels.

Discussion

Our study showed that peripheral total leukocyte, neutrophil, monocyte, and lymphocyte counts were independently associated with hyperuricemia in a dosage-related manner. The association between leukocytes and hyperuricemia persisted even after controlling for conventional risk factors, including age, hypertension, diabetes mellitus, hyperlipidemia, and drinking status. Furthermore, uric acid concentrations were also positively associated with hs-CRP concentrations. These findings are consistent with current evidence suggesting a positive association between inflammatory markers, including WBC count, and the development of hyperuricemia.[11,35]

Previous study reported that the prevalence of hyperuricemia among 282 shift workers at a steel company was 37.5%.[30] Lee et al. found an association between blood lead and

serum uric acid concentrations.[36] In a study conducted in Nigerian lead-exposed workers, people with occupational lead exposure are at risk of developing hyperuricemia and renal impairment.[22] In the present study, the total prevalence of hyperuricemia was 36.9% and the workers who developed hyperuricemia had lower eGFR than that in non-hyperuricemic workers. These findings, therefore, suggest that routine screening of those at risk of occupational lead exposure for increase in serum uric acid or decrease in eGFR may allow early detection and prevention of lead-induced CKD.

Previous studies have documented the association among hyperuricemia, obesity, and metabolic syndrome in adults.[37,38] In particular, increased serum uric acid levels are associated with the risk of cardiovascular or renal diseases.[39,40] Several investigators have shown that insulin resistance plays a central role in the link between metabolic syndrome and hyperuricemia.[41,42] Insulin resistance is thought to cause decreased excretion of uric acid.[43] Previous epidemiological and clinical studies have demonstrated that leukocytosis is an independent predictor of cardiovascular events, stable and unstable angina, myocardial infarction, insulin resistance, type 2 diabetes, and microvascular and macrovascular complications of diabetes.[8] Furthermore, differential cell counts including eosinophil, neutrophil, and monocyte counts have also been shown to be able to predict the future incidence of chronic heart disease.[44] However, no previous study has addressed the correlation between differential leukocyte count and hyperuricemia. Our study, which clearly demonstrated that differential leukocyte counts were independently associated with hyperuricemia, may suggest that leukocytes contribute to the regulation of uric acid homeostasis. Kocaman et al. reported a strong positive independent relationship between serum uric acid and circulating inflammatory cell counts in multiple linear regression analysis.[45] The positive cell counts included WBC, neutrophil, and monocyte counts, but not lymphocyte count. When the patients were divided into four groups according to the quartile of serum uric acid, monocyte count was significantly associated with serum uric acid concentration. Furthermore, Ruggiero et al. also reported relationships between serum uric acid level and CRP and IL-6.[46] In their study, patients with a high uric acid level at baseline had a progressively higher probability of developing clinically relevant increased levels of IL-6 (> 2.5 pg/mL) and CRP (> 3 mg/L) in the following 3 years. In addition, Su et al. showed the association between hyperuricemia and hematological indicators in a Chinese adult population.[11] Nakanishi et al. also demonstrated associations between white blood cell count and features of the metabolic syndrome in Japanese male office workers.[9] In the present study, the subjects with hyperuricemia had higher total and differential leukocyte counts than those without hyperuricemia, and uric acid concentrations were also positively associated with hs-CRP level, implying that serum uric acid has an important pathogenetic role to play in perpetuating inflammatory processes as well as in the development of metabolic and cardiovascular diseases. Therefore, our study may help in the understanding of the mechanism by which hyperuricemia contributes to organ damage.

The mechanism of increased total and differential leukocyte counts in hyperuricemic subjects is a matter of speculation. A plausible hypothesis is that leptin might be involved in the elevation of leukocyte counts.[47] Leptin has been reported to stimulate myeloid differentiation from human bone marrow CD34+ progenitors[48] as well as induce proliferation, differentiation, and functional activation of hemopoietic cells.[47] Previously, Chung et al. reported that plasma leptin concentrations are increased and correlate well with the peripheral leukocyte counts in patients with type 2 DM,[49]

and proposed that leptin may enhance the release and activation of leukocyte from bone marrow and contribute to the leukocytosis in patients with type 2 DM. Furthermore, Bedir et al. showed that leptin appears to be one of the important common parameters in the determination of serum urate levels in overweight and obese individuals and suggested that leptin may be a good candidate for the missing link between obesity and hyperuricemia.[50] The results of the present study support the idea[11,50] that circulating leukocytes may contribute to the development hyperuricemia, partially through the effects of leptin.

There are several limitations to this study. First, since it is a cross-sectional study, a causal association of total and differential leukocyte counts with hyperuricemia could not be established. Second, recall bias may have existed, since smoking, drinking, and exercise habits, and drug therapy were examined through surveys. However, this bias was minimized through comparisons between survey data of identical subjects. Third, as this study is an analysis of a particular group, the results cannot be generalized to all population groups. Further studies including the general population are warranted.

In conclusion, our results indicate significant associations of hyperuricemia with total and differential leukocyte counts, which could be important biological markers of hyperuricemia in male steel workers.

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