ORIGINAL RESEARCH

White Blood Cell Count Is Associated with Hyperuricemia in Patients with Type 2 Diabetes Mellitus

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Background: Hyperuricemia is highly prevalent among patients with type 2 diabetes mellitus (T2DM). Inflammation is associated with the process of hyperuricemia. However, it is unclear whether white blood cell (WBC) count, a convenient inflammatory marker, is associated with hyperuricemia in patients with T2DM. Thus, we aimed to explore the possible association between WBC count and hyperuricemia in patients with T2DM.

Methods: A total of 1768 patients with T2DM were retrospectively included. Cumulative data were analyzed in patients with T2DM.

Results: WBC count was significantly elevated in T2DM patients with hyperuricemia compared with those without hyperuricemia (6.80 [5.60, 8.02] vs 6.20 [5.27, 7.24] 10^9/L, p<0.001). There was a significant positive correlation between WBC count and serum UA levels in patients with T2DM (r=0.165, 95% CI: [0.118, 0.211], p<0.001). Multivariable logistic regression analysis revealed an independent association between WBC count and hyperuricemia in patients with T2DM (OR=1.185, 95% CI: [1.077, 1.303], p<0.001).

Conclusion: Elevated WBC count, even within the normal range, is associated with hyperuricemia in patients with T2DM, suggesting that chronic inflammation, as indicated by a higher WBC count, may be related to the development of hyperuricemia in patients with T2DM and urate-lowering therapy may be helpful to ameliorate chronic inflammatory damage in T2DM patients with hyperuricemia.

Keywords: type 2 diabetes mellitus, hyperuricemia, white blood cell, inflammation

Introduction

Type 2 diabetes mellitus (T2DM) is a disease characterized by impaired insulin secretion or a failure of tissues to respond to insulin.[1] The prevalence of T2DM maintains an increased trend globally, and the escalating burden of T2DM has become a significant concern within the healthcare domain.[2] The chronic complications of T2DM mainly include macrovascular and microvascular manifestations, such as cardiovascular disease, retinopathy, nephropathy, and neuropathy, which seriously affect patient's quality of life.[3,4] Hyperuricemia, a purine metabolic disorder, has emerged as a significant public health burden.[5] Accumulating evidences have reported that the prevalence of hyperuricemia is high among patients with T2DM.[6–8] It has been suggested that inflammation is associated with in the process of hyperuricemia.[9]

White blood cell (WBC) count is a convenient marker for assessing inflammation.[10] The variations in WBC subtypes have been associated with multiple diseases, including coronary heart disease, ischemic stroke, and cancer.[11–13] Convincing evidence has demonstrated that WBC count is positively correlated with uric acid (UA) in patients with preeclampsia.[14] It has been found that WBC count is positively associated with elevated serum UA levels in females who live in high-altitude

regions.[15] There has been a positive correlation between WBC count and serum UA levels in adolescents with hyperuricemia.[16] In addition, an increased WBC count has been proposed as an important biological marker of hyperuricemia in an adult population.[17] Even more importantly, an elevated WBC count has been reported to be associated with hyperuricemia independently of conventional risk factors for chronic kidney disease,[18] though the mechanism of inflammation is a crucial factor in kidney injury.[19] However, to our knowledge, the association between WBC count and hyperuricemia still remains unknown in patients with T2DM. Hence, the aim of this study was to examine the possible association between WBC count and hyperuricemia in patients with T2DM.

Methods

Patients

A total of 1768 T2DM patients who visited the National Metabolic Management Center, Zhongda Hospital, Southeast University were retrospectively included from January 2021 to March 2023. The diagnosis of T2DM was determined according to the American Diabetes Association criteria.[20] Hyperuricemia was defined as serum UA levels >420 μmol/L in males and >360 μmol/L in females.[21] To minimize potential factors that affected WBC count, T2DM patients with a WBC count outside the normal range were excluded from the study. Moreover, T2DM patients with missing data for the included variables were also excluded from the analysis. The study was approved by the Ethics Committee of Zhongda Hospital, Southeast University, and was conducted in compliance with the Declaration of Helsinki. Due to the retrospective nature of this study, the requirement for informed consent of patients was waived by the Ethics Committee of Zhongda Hospital, Southeast University. The data of patients were maintained with confidentiality.

Data Extraction

We extracted the following data: (a) sex, age, height, and weight; (b) medical history; (c) the results of laboratory examinations including WBC count, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr), and UA. The laboratory examinations were carried out after overnight fasting. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meter.

Statistical Analysis

Continuous variables are expressed as median and interquartile range due to non-normally distribution, and categorical variables are expressed as frequency and percentage. Chi-square test was employed to compare the differences in categorical variables, and Mann–Whitney U-test was used to compare the differences in continuous variables. Spearman correlation analysis was used to assess the correlation between the two continuous variables. Univariable logistic regression analysis was used to examine which variables were associated with hyperuricemia in patients with T2DM. Multivariable logistic regression analysis was performed to determine the independent factors associated with hyperuricemia in patients with T2DM. A p value of 0.05 was considered to indicate statistical significance. The data were analyzed by SPSS version 29.0 (IBM, Corporation, Armonk, NY, USA).

Results

The Characteristics of T2DM Patients With Hyperuricemia and Those Without Hyperuricemia

The characteristics were compared between T2DM patients with hyperuricemia and those without hyperuricemia (Table 1). WBC count was significantly higher in T2DM patients with hyperuricemia than in those without hyperuricemia (6.80 [5.60, 8.02] vs 6.20 [5.27, 7.24] 10^9/L, p<0.001). Moreover, there were significant differences with respect to age (p=0.002), BMI (p<0.001), hypertension history (p<0.001), TG (p<0.001), HDL-C (p<0.001), and Cr (p<0.001) between the groups. No significant differences were observed in gender (p=0.287), coronary heart disease history (p=0.105), FBG (p=0.144), HbA1c (p=0.208), TC (p=0.661), and LDL-C (p=0.120) between the groups.

Table 1 The Characteristics of T2DM Patients with Hyperuricemia and Those without Hyperuricemia

Variables	T2DM Patients with Hyperuricemia N=291	T2DM Patients without Hyperuricemia N=1477	p value
Males (n, %)	175(60.1)	937(63.4)	0.287
Age (years)	57(45, 64)	59(51, 65)	0.002
Body mass index (kg/m^2)	26.2(24.1, 29.4)	24.8(22.8, 27.1)	<0.001
Coronary heart disease history (n, %)	44(15.1)	173(11.7)	0.105
Hypertension history (n, %)	186(63.9)	712(48.2)	<0.001
Fasting blood glucose (mmol/L)	7.60(6.16, 10.50)	8.09(6.29, 11.23)	0.144
Hemoglobin A1c (%)	8.57(7.04, 10.50)	8.82(7.33, 10.40)	0.208
Total cholesterol (mmol/L)	4.45(3.81, 5.23)	4.48(3.69, 5.22)	0.661
Triglyceride (mmol/L)	1.87(1.34, 2.96)	1.33(0.94, 1.98)	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.01(0.82, 1.18)	1.12(0.93, 1.31)	<0.001
Low-density lipoprotein cholesterol (mmol/L)	2.48(1.84, 2.98)	2.54(1.94, 3.10)	0.120
Creatinine (umol/L)	74(58, 94)	62(52, 74)	<0.001
White blood cell count (10^9/L)	6.80(5.60, 8.02)	6.20(5.27, 7.24)	<0.001

Abbreviation: T2DM, type 2 diabetes mellitus.

The Correlation Between WBC Count and Serum UA Levels in Patients With T2DM

The correlation analysis between WBC count and continuous variables was conducted in patients with T2DM (Table 2). WBC count was significantly positively correlated with serum UA levels in patients with T2DM (r=0.165, 95% CI: [0.118, 0.211], p<0.001) (Figure 1). WBC count was also found to be significantly positively correlated with BMI (r=0.141, 95% CI: [0.094, 0.188], p<0.001), FBG (r=0.093, 95% CI: [0.045, 0.140], p<0.001), HbA1c (r=0.095, 95% CI: [0.047, 0.142], p<0.001), TG (r=0.156, 95% CI: [0.109, 0.203], p<0.001), and Cr (r=0.081, 95% CI: [0.033, 0.128], p<0.001), and significantly negatively correlated with age (r=−0.083, 95% CI: [−0.130,-0.035], p<0.001) and HDL-C (r=−0.164, 95% CI: [−0.210,-0.117], p<0.001) except for TC (r=0.011, 95% CI: [−0.037, 0.059], p=0.648) and LDL-C (r=0.003, 95% CI: [−0.045, 0.051], p=0.899) in patients with T2DM.

The Independent Association Between WBC Count and Hyperuricemia in Patients With T2DM

The univariable and multivariable logistic regression analyses were conducted in patients with T2DM (Table 3). Univariable logistic regression analysis found that WBC ount (OR=1.279, 95% CI: [1.170, 1.399], p<0.001), age

Table 2 The Correlation Between WBC Count and Continuous Variables in Patients with T2DM

Variables	r	95% CI	p value
Age	−0.083	(−0.130,-0.035)	<0.001
Body mass index	0.141	(0.094, 0.188)	<0.001
Fasting blood glucose	0.093	(0.045, 0.140)	<0.001
Hemoglobin A1c	0.095	(0.047, 0.142)	<0.001
Total cholesterol	0.011	(−0.037, 0.059)	0.648
Triglyceride	0.156	(0.109, 0.203)	<0.001
High-density lipoprotein cholesterol	−0.164	(−0.210,-0.117)	<0.001
Low-density lipoprotein cholesterol	0.003	(−0.045, 0.051)	0.899
Creatinine	0.081	(0.033, 0.128)	<0.001
Uric Acid	0.165	(0.118, 0.211)	<0.001

Abbreviations: WBC, white blood cell; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.
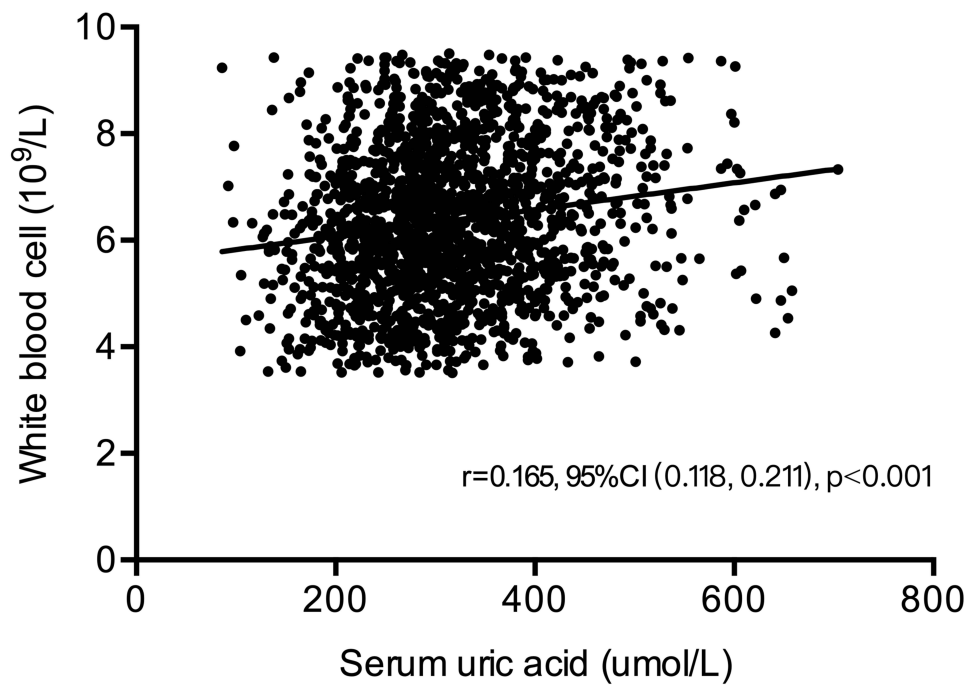
Figure 1 The correlation between WBC count and UA in patients with T2DM.
Abbreviation: WBC, white blood cell; UA, uric acid; T2DM, type 2 diabetes mellitus; CI, confidence interval.

(OR=0.978, 95% CI: [0.968, 0.989], p<0.001), BMI (OR=1.118, 95% CI: [1.084, 1.154], p<0.001), hypertension history (OR=1.903, 95% CI: [1.467, 2.469], p<0.001), TG (OR=1.098, 95% CI: [1.053, 1.146], p<0.001), HDL-C (OR=0.252, 95% CI: [0.159, 0.398], p<0.001), and Cr (OR=1.011, 95% CI: [1.007, 1.015], p<0.001) were significantly associated with hyperuricemia in patients with T2DM. After adjustment for gender, age, BMI, coronary heart disease history, hypertension history, FBG, HbA1c, TC, TG, HDL-C, LDL-C, and Cr, multivariable logistic regression analysis revealed that WBC count was independently associated with hyperuricemia in patients with T2DM (OR=1.185, 95% CI: [1.077, 1.303], p<0.001), and that gender (OR=0.535, 95% CI: [0.394, 0.727], p<0.001), age (OR=0.973, 95% CI: [0.960,

Table 3 Univariable and Multivariable Logistic Regression Analyses of Factors Associated with Hyperuricemia in Patients with T2DM

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Males	0.869(0.672, 1.125)	0.287	0.535(0.394, 0.727)	<0.001
Age	0.978(0.968, 0.989)	<0.001	0.973(0.960, 0.986)	<0.001
Body mass index	1.118(1.084, 1.154)	<0.001	1.054(1.017, 1.092)	0.004
Coronary heart disease history	1.343(0.939, 1.920)	0.106	1.225(0.817, 1.837)	0.326
Hypertension history	1.903(1.467, 2.469)	<0.001	1.761(1.300, 2.386)	<0.001
Fasting blood glucose	0.983(0.955, 1.012)	0.239	0.973(0.940, 1.006)	0.111
Hemoglobin A1c	0.961(0.905, 1.020)	0.194	0.955(0.888, 1.027)	0.219
Total cholesterol	1.023(0.932, 1.122)	0.636	0.805(0.632, 1.026)	0.079
Triglyceride	1.098(1.053, 1.146)	<0.001	1.138(1.054, 1.228)	<0.001
High-density lipoprotein cholesterol	0.252(0.159, 0.398)	<0.001	0.414(0.239, 0.717)	0.002
Low-density lipoprotein cholesterol	0.878(0.760, 1.015)	0.078	1.427(1.044, 1.949)	0.026
Creatinine	1.011(1.007, 1.015)	<0.001	1.012(1.008, 1.017)	<0.001
White blood cell count	1.279(1.170, 1.399)	<0.001	1.185(1.077, 1.303)	<0.001

Abbreviations: T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

0.986], p<0.001), BMI (OR=1.054, 95% CI: [1.017, 1.092], p=0.004), hypertension history (OR=1.761, 95% CI: [1.300, 2.386], p<0.001), TG (OR=1.138, 95% CI: [1.054, 1.228], p<0.001), HDL-C (OR=0.414, 95% CI: [0.239, 0.717], p=0.002), LDL-C (OR=1.427, 95% CI: [1.044, 1.949], p=0.026), and Cr (OR=1.012, 95% CI: [1.008, 1.017], p<0.001) were also as factors independently associated with hyperuricemia in patients with T2DM.

Discussion

WBC count is a component of complete blood count. Our study revealed that elevated WBC count, although still within the normal range, was independently associated with hyperuricemia in patients with T2DM. WBC count, even within the normal range, is widely acknowledged to be an indicator of inflammation.[10] Thus, inflammatory mechanism may mediate the association between elevated WBC count and hyperuricemia in patients with T2DM. Ruggiero C et al[22] suggested a significant positive association between UA and inflammatory markers such as tumor necrosis factor-α, interleukin-6, and interleukin-18 in community-dwelling older persons. High-sensitivity C-reactive protein levels have been reported to be positively associated with the prevalence of hyperuricemia.[23] It has been confirmed that urate-lowering therapy improves systemic inflammation by reducing UA in asymptomatic hyperuricemia.[24] Thus, these literatures suggest that UA may activate the inflammatory response through different mechanisms. Indeed, UA triggers the inflammatory response by affecting immune cells in a hyperuricemic environment.[9] UA can promote the inflammation by several intracellular signaling pathways, including ERK/p38 MAPK, AMPK, and PI3K,[25] and may also induce renal inflammation by NF-κB signaling activation.[26] Additional, hyperuricemia establishes a pro-inflammatory microenvironment through multiple signaling pathways, including NLRP3 inflammasome activation, JAK2/STAT3 cascade, and ROS/NRLP3/NF-κB axis.[27–29] Notably, elevated levels of UA promote the formation of monosodium urate (MSU) crystals in circulation.[30] Thus, the inflammatory effects of UA also depend on its precipitation into MSU crystals in the development of gout.[31] Mechanistically, MSU crystals induce the production of active interleukin-1β and interleukin-18 by activating NALP3 inflammasome.[32] Furthermore, MSU crystals directly stimulate tumor necrosis factor-α synthesis,[33] and activateboth classical and alternative complement pathways to amplify inflammatory response.[34,35] Emerging evidence indicates that MSU crystal deposits induce inflammatory response through innate immune cellular recognition for naked MSU crystals via specific Toll-like receptors.[36] Thus, these molecular mechanisms collectively underscore that the formation of MSU crystals is an important factor for the inflammatory response in T2DM patients with hyperuricemia.

Established epidemiological evidence has confirmed that female gender, high BMI, and reduced estimated glomerular filtration rate are associated with hyperuricemia in patients with T2DM.[37] Our results identified that female gender, high BMI, and high Cr were independently associated with hyperuricemia in patients with T2DM. Hyperuricemia has been shown to be associated with an increased risk for incident hypertension.[38] Our study observed an independent association between hypertension history and hyperuricemia in patients with T2DM. Moreover, the current investigation aslo found that younger age, high TG, high LDL-C, and low HDL-C were independently associated with hyperuricemia in our study cohort.

The study has several limitations. First, the cross-sectional design inherently precludes causal inference between WBC count and hyperuricemia in patients with T2DM. Second, the association between other inflammatory markers, such as C-reactive protein, and hyperuricemia was not estimated in patients with T2DM. Third, longitudinal changes in the WBC count following urate-lowering therapy remain unknown due to the absence of interventional follow-up in T2DM patients with hyperuricemia. Fourth, residual confounders from unmeasured variables including dietary patterns, pharmacological exposures, and selection bias may infuence the observed results.

In conclusion, the study demonstrates an association between elevated WBC count, even within physiologically normal limits, and hyperuricemia in patients with T2DM. The findings suggest that chronic inflammation, reflected by increased WBC count, likely contributes to the development of hyperuricemia in patients with T2DM. Importantly, the observations support that urate-lowering therapy may offer benefits in alleviating chronic inflammatory damage in T2DM patients with hyperuricemia.

Data Sharing Statement

Data are available upon reasonable request from the corresponding author.

Ethics Approval

The study was approved by the Ethics Committee of Zhongda Hospital, Southeast University, and was conducted in compliance with the Declaration of Helsinki. Due to the retrospective nature of this study, the requirement for informed consent of patients was waived by the Ethics Committee of Zhongda Hospital, Southeast University. The data of patients were maintained with confidentiality.

Disclosure

The authors report no conflicts of interest in this work.

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