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## **Association between weight-adjusted-waist index and serum ferritin in patients with type 2 diabetes**

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## ABSTRACT

**Background and Objectives:** To investigate the correlation between weight-adjusted-waist index (WWI), a novel obesity index, and serum ferritin (SF) level in patients with type 2 diabetes mellitus (T2DM), and the association between WWI and the prevalence of hyperferritinemia. **Methods and Study Design:** A total of 943 patients with T2DM were divided into three groups based on WWI tertile levels. Disparities in SF levels and the prevalence of hyperferritinemia were compared among these groups. The correlations among WWI, SF levels, and hyperferritinemia were analyzed in patients with T2DM. **Results:** As WWI tertile levels increased, SF levels tended to increase ( $p$  for trend  $<0.01$ ). A statistically significant positive correlation was observed between the WWI and SF levels ( $R = 0.263$ ,  $p < 0.001$ ). After adjusting for confounders by multiple linear regression, a significant positive correlation was maintained between the WWI and SF levels [ $\beta = 0.194$ , 95% CI (49.914, 112.120)],  $p < 0.01$ ]. Binary logistic regression analysis revealed a positive association between the WWI and the likelihood of hyperferritinemia, with a notably stronger correlation observed in females compared to males [OR = 3.248, 95% CI (2.027, 5.204),  $p < 0.01$  vs. OR = 2.091, 95% CI (1.432, 3.054),  $p < 0.01$ ]. **Conclusions:** Along with increasing WWI, SF levels gradually increased in patients with T2DM. The WWI exhibited a positive correlation with SF levels and hyperferritinemia, more significantly in female patients.

**Key Words:** weight-adjusted-waist index, serum ferritin, hyperferritinemia, type 2 diabetes; obesity

## INTRODUCTION

With rapid socioeconomic development and changes in diet and lifestyle, diabetes has become a significant global health issue. Globally, 537 million patients with diabetes account for approximately 10.5% of the population. By 2030, the number of patients with diabetes is projected to increase to 643 million, reaching 783 million by 2045, representing a 46% increase.<sup>1</sup> Obesity increases synchronously with diabetes and exacerbates health threats. From 1990–2021, global obesity contributed to a 24.3% increase in disability-adjusted life years in patients with type 2 diabetes mellitus (T2DM).<sup>2</sup>

A prospective study among Chinese adults indicated that approximately 24.4% of diabetes risk is attributed to insulin resistance, while only 12.4% is linked to  $\beta$ -cell dysfunction. This suggests that insulin resistance has a greater impact on diabetes occurrence and development in Chinese adults, doubling that of  $\beta$ -cell dysfunction and tripling to 3.5 times in obese

individuals. Scholars have proposed that a chronic inflammatory state is a potential mechanism for insulin resistance development in patients with obesity and T2DM, particularly in individuals with visceral obesity. Fat deposition in the liver and pancreas, along with inflammatory molecules (adipokines) secreted by adipose tissue, negatively affects insulin sensitivity in the liver and other tissues.<sup>3</sup>

Body mass index (BMI) is commonly used to assess obesity. However, BMI cannot effectively distinguish between the distributions of muscle and fat mass. The weight-adjusted-waist index (WWI) is a new anthropometric index. According to the calculation of waist circumference (cm) divided by the square root of body weight (kg), waist circumference and weight can be standardized to reflect adverse metabolic components, such as high fat mass, low muscle mass, and low bone mass, and to better evaluate central obesity independent of body weight.<sup>4</sup> Recent studies have reported that an increased WWI is associated with new-onset diabetes.<sup>5</sup> Furthermore, several studies have revealed that the WWI is positively correlated with the risk of hyperuricemia and a variety of cardiocerebrovascular events, including stroke, coronary heart disease, heart failure left ventricular hypertrophy, and abdominal aortic calcification.<sup>6-11</sup>

Serum ferritin (SF), the principal repository of stored iron within the body, plays crucial roles in iron homeostasis, maintaining cell function, and protecting proteins from potential iron toxicity.<sup>12</sup> Iron overload in the body increases the risk of chronic metabolic diseases, such as diabetes, by affecting insulin sensitivity.<sup>13</sup> Several studies have demonstrated a close association between SF levels and fasting plasma glucose, insulin resistance the risk of diabetes, and nonalcoholic fatty liver disease.<sup>14-17</sup> In clinical practice, ferritin is primarily used as a serum marker to reflect overall iron storage and inflammatory status.<sup>18</sup>

With an increased understanding of micronutrients, further research on the role of iron metabolism in glucose and lipid metabolism is required. The WWI is a useful index for evaluating central obesity. To date, no study has investigated the correlation between the WWI and SF levels in patients with T2DM. Therefore, this study aimed to explore the associations among the WWI, SF levels, and the prevalence of hyperferritinemia in patients with T2DM.

## **MATERIALS AND METHODS**

### ***Study population***

Initially, 1633 patients with T2DM admitted to the Department of Endocrinology at a university hospital between March 2022 and March 2023 were considered for the study. Upon

application of the predefined inclusion and exclusion criteria, 943 patients with T2DM were enrolled into the study. This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the First Hospital of Lanzhou University (2024-04-28/LDYILL2024-315). Informed consent Written informed consent was obtained from all participants.

### ***Inclusion criteria***

Patients were over eighteen years of age and of Han ethnicity, met the World Health Organization (WHO) T2DM diagnostic criteria, and had complete clinical information and data.

### ***Exclusion criteria***

(1) Individuals diagnosed with type 1 diabetes, gestational diabetes, or another distinctive form of diabetes; (2) acute complications related to diabetes, including hyperosmolar hyperglycemia or diabetic ketoacidosis; (3) acute infection; (4) malignant tumors and autoimmune diseases; (5) severe heart disease defined as heart failure; (6) kidney disease defined by an eGFR  $<30 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ , or renal insufficiency necessitating renal replacement therapy; (7) liver disease defined by AST/ALT levels  $> 3$  times the upper limit of normal; (8) hematologic disorders, including anemia (hemoglobin concentration below 120 g/L for adult males and below 110 g/L for adult females); (9) treatment with steroids, iron supplements, or blood transfusions recently; and (10) incomplete clinical data.

### ***General characteristics of the study participants***

Demographic and clinical information, including sex, age, diabetes duration, personal habits including smoking and alcohol consumption, menopausal status for female patients, past medical history, and medication usage, was extracted from medical records. Height, weight, waist circumference, hip circumference, and blood pressure were measured and recorded.

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$$

$$\text{Weight-adjusted-waist index (WWI)} = \text{waist circumference (cm)}/\text{weight (kg)}^{1/2}$$

### ***Laboratory examinations***

Following an 8-hour fasting period, 5 mL of venous blood was collected from all participants in the morning, and the serum was isolated. The alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting plasma glucose (FPG), total cholesterol (TC), serum

triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured using an automatic biochemical analyzer (BS-220, Shenzhen Miabio, Guangdong Province). Glycated hemoglobin (HbA1c) levels were measured by high-performance liquid chromatography (Bio-Rad-D10; Bio-Rad Laboratories). Fasting insulin (FINS) and fasting C-peptide (FCP) levels were measured using a chemiluminescent immunoassay analyzer (CENTAUR-XP Automated Chemiluminescent Immunoassay Analyzer; Siemens Healthineers).

$$\text{HOMA-IR} = \text{FINS} \times \text{FPG} / 22.5$$

### ***Body composition measurement***

The distribution of abdominal fat was assessed by measuring the abdominal visceral fat area (VFA) and abdominal subcutaneous fat area (SFA) using an OsteoSys EXA-3000 dual-energy X-ray device.

### ***Diagnostic criteria of disease***

T2DM diagnoses were determined based on the World Health Organization's (WHO) 1999 diagnostic criteria.

Hyperferritinemia was defined as SF levels  $\geq 300$  ng/mL for adult males or  $\geq 150$  ng/mL for adult females.<sup>19,20</sup>

Nonalcoholic fatty liver disease (NAFLD) was diagnosed by abdominal ultrasound examination by an experienced sonographer. The presence of two of the following abdominal ultrasound features suggests diffuse fatty liver: (1) the near-field echo of the liver demonstrates diffuse enhancement, which is more intense than that of the kidneys and spleen; (2) indistinct intrahepatic ductal structures; and (3) gradual weakening of the liver's far-field echo.

### ***Study population grouping***

The patients were divided into T1 (WWI < 10.77), T2 ( $10.77 \leq \text{WWI} < 11.28$ ), and T3 (WWI  $\geq 11.28$ ) groups based on the tertile levels of the WWI. Differences in SF levels and the prevalence of hyperferritinemia were compared among the groups.

### ***Statistical methods***

All the data were subjected to statistical analysis using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp.). The Shapiro–Wilk test was used to test normality. Normally

distributed measurement data are expressed as the mean  $\pm$  standard deviation ( $\bar{x}\pm s$ ), while nonnormally distributed measures are expressed as medians and quartiles [M (P25, P75)]. One-way analysis of variance (ANOVA) was used for normally distributed data to analyze independent samples, and the Kruskal–Wallis nonparametric test was used for nonnormally distributed data. Bonferroni correction was applied for pairwise comparisons. The Bonferroni correction was used to compare the two groups. Enumeration data are presented as frequencies and percentages (%). The chi-square test was used to compare the differences between groups, and the Bonferroni correction was used to compare the differences between two groups via the z test to adjust the p values. Linear-by-linear association tests and the Jonckheere-Terpstra test were used to analyze trends between groups. Correlation analyses were performed using Pearson or Spearman's rank correlation analysis. Independent correlations between the WWI and SF levels were explored using multiple linear regression analyses. Additionally, linear trend analysis was performed by incorporating the median values of each WWI category as continuous variables within the model. The association between the WWI and hyperferritinemia was investigated using binary logistic regression analysis. A significance level of  $p < 0.05$  was considered to indicate statistical significance.

## RESULTS

### *Baseline characteristics according to WWI tertile group*

Significant increasing trends were observed for age, weight, hypertension prevalence, SBP, WC, HC, BMI, SF, HbA1c, HOMA-IR, FCP, FINS, TG, LDL-C, HDL-C, SFA, VFA, and NAFLD prevalence (all  $p$  for trend  $< 0.05$ ), while a decreasing trend in height and HDL-C was found with an increase in WWI tertile levels ( $p$  for trend  $< 0.05$ ). No significant differences were found in the duration of diabetes, menopausal status, smoking history, drinking history, FPG, or TC levels among the groups ( $p > 0.05$ ) (Table 1).

In male patients, the SF level in the T3 group (228.79 ng/mL) was significantly higher than that in the T1 group (147.00 ng/mL,  $p < 0.01$ ). In females, the median SF concentration in the T3 group was 172.50 ng/mL, marking a significant increase relative to the median concentrations observed in the T1 and T2 groups, which were 84.10 ng/mL and 120.00 ng/mL, respectively (both  $p < 0.05$ ). Regardless of sex, as the WWI tertiles increased, the SF levels exhibited an increasing trend ( $p$  for trend  $< 0.01$ ). Hyperferritinemia prevalence in the T3 group (37.3%) was significantly higher than that in the T1 and T2 groups (27.2% and 18.5%, respectively; both  $p < 0.01$ ), and the T2 group also exhibited a higher prevalence of hyperferritinemia than the T1 group ( $p < 0.01$ ) in male patients. In female patients,

hyperferritinemia prevalence in the T3 group (57.7%) was also significantly higher than that in the T1 group (16.9%,  $p < 0.01$ ) (Table 1).

### ***Comparison of glucose and lipid metabolism indicators between the hyperferritinemia and non-hyperferritinemia groups***

The glucose and lipid metabolism indicators, including HbA1c, HOMA-IR, TC, TG, and LDL-C, were compared between the hyperferritinemia and non-hyperferritinemia groups. HbA1c levels were significantly higher in the hyperferritinemia group [8.50 (7.00, 10.70)] than in the non-hyperferritinemia group [8.10 (6.75, 9.40)] ( $p=0.001$ ) indicating poorer glycemic control in individuals with hyperferritinemia. Similarly, HOMA-IR, a marker of insulin resistance, was significantly elevated in the hyperferritinemia group [2.41 (1.51, 4.05)] compared to the non-hyperferritinemia group [2.10 (1.25, 3.71)] ( $p=0.017$ ).

In terms of lipid metabolism, the hyperferritinemia group showed significantly higher TC levels [4.28 (3.67, 4.90)] compared to the non-hyperferritinemia group [4.06 (3.39, 4.76)] ( $p=0.004$ ). TG levels were also significantly elevated in the hyperferritinemia group [1.75 (1.27, 2.61)] compared to the non-hyperferritinemia group [1.50 (1.09, 2.19)] ( $p < 0.001$ ). LDL-C levels followed the same trend, with significantly higher values in the hyperferritinemia group [1.50 (1.09, 2.19)] compared to the non-hyperferritinemia group [2.72 (2.20, 3.31)] ( $p=0.001$ ). (Figure 1)

### ***Correlation analysis of the WWI with other clinical indices***

There was a positive correlation between the WWI and SF levels in patients with T2DM ( $R=0.263$ ,  $p < 0.01$ ). The WWI was positively correlated with age, menopause status, hypertension status, BMI, WC, HC, SBP, SF, HbA1c, HOMA-IR, FCP, FINS, TG, LDL-C, SFA, VFA, and the prevalence of NAFLD ( $p < 0.05$ ) but negatively correlated with height and HDL-C ( $p < 0.01$ ). There were no significant correlations between the WWI and duration of diabetes, history of drinking or smoking, weight, DBP, FPG, or TC ( $p > 0.05$ ) (Table 2).

### ***Association between the WWI and SF levels***

Multiple linear regression analysis was conducted, employing SF levels as the dependent variable and the WWI as the independent variable. For this analysis, the T1 group was designated as the reference group.

In Model 1, after adjusting for age, sex, duration of diabetes, BMI, SBP, and DBP, the WWI was associated with SF levels in the T2 and T3 groups [ $\beta = 0.147$ , 95% CI (18.324, 51.604),  $p < 0.001$  and  $\beta = 0.221$ , 95% CI (61.651, 123.151),  $p < 0.001$ , respectively].

In Model 2, after further adjustments for HbA1c, HOMA-IR, FCP, and FINS, the WWI remained independently correlated with SF levels in the T2 and T3 groups [ $\beta = 0.132$ , 95% CI (14.912, 47.990),  $p < 0.001$  and  $\beta = 0.199$ , 95% CI (52.329, 113.652),  $p < 0.001$ , respectively].

After adjusting for TG, HDL-C, LDL-C, SFA, and VFA in Model 3, the WWI maintained a significant, positive, independent correlation with SF levels in both T2 and T3 groups [ $\beta = 0.126$ , 95% CI (13.642, 46.543),  $p < 0.001$  and  $\beta = 0.194$ , 95% CI (49.914, 112.12),  $p < 0.001$ , respectively].

As the tertiles of WWI increased, their association with SF became stronger ( $p$  for trend  $< 0.01$ ) (Table 3).

### ***Association between the WWI and hyperferritinemia***

Binary logistic regression analysis was conducted to evaluate the association between hyperferritinemia and the WWI. The hyperferritinemia considered as the dependent variable.

In male patients with T2DM, after adjusting for age, duration of diabetes, BMI, and hypertension, the WWI remained a significant independent risk factor for hyperferritinemia [OR = 2.209, 95% CI (1.538, 3.172),  $p < 0.001$ ]. In Model 2, after further adjustments for HbA1c, FINS, FCP, and HOMA-IR, the WWI continued to be an independent risk factor for hyperferritinemia [OR = 2.137, 95% CI (1.478, 3.090),  $p < 0.001$ ]. HbA1c levels also demonstrated a significant positive correlation with hyperferritinemia [OR = 1.139, 95% CI (1.041, 1.245),  $p < 0.01$ ]. Finally, after further adjustments for TG, HDL-C, LDL-C, SFA, and VFA, the WWI remained a significant independent risk factor for hyperferritinemia [OR = 2.091, 95% CI (1.432, 3.054),  $p < 0.001$ ]. HbA1c and TG levels were positively correlated with hyperferritinemia [OR = 1.134, 95% CI (1.035, 1.242),  $p < 0.01$ ; OR = 1.103, 95% CI (1.002, 1.214),  $p < 0.05$ , respectively]. Age was negatively correlated with hyperferritinemia [OR = 0.960, 95% CI (0.942, 0.979),  $p < 0.001$ ].

In female patients with T2DM, after adjusting for age, diabetes duration, BMI, and hypertension, the WWI also remained an independent risk factor for hyperferritinemia [OR = 3.485, 95% CI (2.210, 5.497),  $p < 0.001$ ]. In Model 2, after further adjustments for HbA1c, FINS, FCP, and HOMA-IR, the WWI continued to be a significant risk factor for hyperferritinemia [OR = 3.425, 95% CI (2.158, 5.438),  $p < 0.001$ ]. HbA1c levels showed a positive correlation with hyperferritinemia [OR = 1.202, 95% CI (1.054, 1.371),  $p < 0.01$ ].



After further adjustment for TG, HDL-C, LDL-C, SFA, and VFA, the WWI remained a significant independent risk factor for hyperferritinemia [OR = 3.248, 95% CI (2.027, 5.204),  $p < 0.001$ ]. HbA1c levels were still correlated with hyperferritinemia [OR = 1.211, 95% CI (1.055, 1.390),  $p < 0.01$ ]. (Table 4).

## DISCUSSION

Given the important role of obesity in the occurrence and development of T2DM and the increased understanding of trace elements, several studies have focused on the association between new obesity indicators and metabolic disorders. The WWI was first introduced in 2018 as a novel indicator for assessing central obesity with the advantage of its simple calculation.<sup>21</sup> Research has shown that the WWI is associated with unhealthy body composition and adverse metabolic outcomes and often serves as a comprehensive predictor of the onset and mortality of metabolic diseases.<sup>22</sup> The correlation between the WWI and SF levels in patients with T2DM has not been previously reported currently. The present study revealed a significant positive correlation between the WWI and SF levels in patients with T2DM.

Prior investigations have demonstrated a significant positive association between BMI and SF levels, with a concomitant increase in the prevalence of hyperferritinemia as BMI increases.<sup>23,24</sup> Nevertheless, the ability of BMI to precisely delineate adipose tissue distribution is limited. BMI cannot identify the presence of abdominal and visceral obesity, which are critical factors for understanding the association between adipose tissue function and iron metabolism. SF levels exhibit positive correlations with adipose tissue insulin resistance, visceral adiposity index, and lipid accumulation.<sup>25</sup> Elevated SF concentrations have been found to be positively correlated with the amount of visceral fat tissue.<sup>26</sup> Pathophysiological changes in adipose tissue and the activation of inflammatory cell populations, including neutrophils, monocytes, lymphocytes, and tissue-resident macrophages, lead to elevated levels of inflammatory biomarkers in the plasma and an increased number of circulating inflammatory cells. Within adipose tissue, the release of various inflammatory mediators, such as TNF- $\alpha$  and IL-6, further stimulates the production of C-reactive protein. Concurrently, a decrease in the secretion of the anti-inflammatory adipokine adiponectin contributes to the establishment of a proinflammatory environment.<sup>27</sup> Additionally, inflammatory and adipose factors may lead to elevated hepcidin levels, thereby enhancing intestinal iron absorption and hepatic release and resulting in increased SF levels.<sup>28</sup>

Therefore, SF may serve as a pivotal biomarker for the early detection of adipose tissue dysfunction in obese individuals. Our research revealed a gradual increase in SF levels with increasing WWI. After adjusting for potential confounders, the WWI remained an independent risk factor for hyperferritinemia. Our findings are congruent with the outcomes reported by Han et al, indicating that the WWI is positively correlated with SF levels in American adults.<sup>29</sup> WWI shows the potential to assess the impact of adipose tissue on SF levels. But further research is needed to compare WWI with BMI and other measures of fat accumulation to confirm its advantage in accuracy.

In patients with T2DM, the association between the WWI and SF primarily focuses on aberrations in glucose and lipid metabolism. In terms of glucose metabolism, an increase in the tertile levels of WWI, HbA1c, FPG, HOMA-IR, FCP, and FINS exhibited an upward trend. Obesity is a well-known risk factor for insulin resistance in individuals with diabetes. Dysfunction within adipose tissue triggers an escalation of proinflammatory cytokines and chemokines, promotes immune cell infiltration, and fosters the accumulation of senescent cells. These alterations culminate in insulin resistance, perpetuation of chronic sterile inflammation, and dysregulation of lipid distribution.<sup>30</sup> The contribution of central obesity to diabetes has become a growing concern. As a reliable indicator of central obesity, the WWI has been confirmed by some studies to be an independent risk factor for T2DM. A prospective cohort study conducted in rural Chinese populations revealed a noteworthy correlation between the incidence of T2DM and the WWI. Compared with that in the lowest WWI quartile group, the risk of T2DM in men and women in the highest WWI quartile group increased by 1.604 and 1.899 times, respectively.<sup>5</sup> A cross-sectional study using NHANES data revealed a notable positive correlation between the WWI and the risk of T2DM in American adults. For each additional increase in the WWI, the risk of developing T2DM increased by 1.14 times (OR = 2.14, 95% CI [1.98, 2.31],  $p < 0.001$ ).<sup>31</sup>

Many previous studies have demonstrated that increased iron is closely associated with adverse health outcomes, particularly with metabolic diseases. In this study, participants were divided into two groups based on serum ferritin levels. Compared to the non-hyperferritinemia group, patients in the hyperferritinemia group exhibited higher levels of HbA1c, HOMA-IR, TC, TG, and LDL-c. A prospective cohort study carried out by Chen et al. among the Chinese population demonstrated that serum ferritin levels were associated with an elevated risk of type 2 diabetes. This association was independent of traditional risk factors, the hazard ratios for incident diabetes corresponding to one standard deviation increase in serum ferritin levels were 1.17.<sup>32</sup> Another cross-sectional study based on a cohort of 1,928

Middle Eastern individuals showed a significant association between serum ferritin levels and dyslipidemia, impaired glucose tolerance, and metabolic syndrome.<sup>33</sup> Iron load may play a role in the development of T2DM by affecting insulin secretion, insulin resistance, and other interconnected pathways.<sup>13,34-36</sup> Iron overload can increase the production of reactive oxygen species (ROS), lead to oxidative stress damage, and induce oxidative damage in islet  $\beta$  cells, resulting in a decrease in insulin synthesis and secretion.<sup>37</sup> Additionally, the coupling of glucose metabolism and insulin release also depends on the involvement of iron. Iron, an important coenzyme in the tricarboxylic acid cycle, participates in the glycosylation reduction pathway and affects glucose metabolism and insulin secretion.<sup>38</sup> In contrast, SF has a direct lipolytic effect on adipocytes, which leads to an excess of circulating free fatty acids and insulin resistance.<sup>39</sup>

Furthermore, patients with a higher WWI exhibited a higher prevalence of metabolic disorders, including hypertension, abnormal blood lipid levels, and NAFLD. Metabolic syndrome (MetS) is a multifaceted metabolic disorder characterized by the concurrent presence of abdominal obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension.<sup>40</sup> Epidemiological studies have revealed a correlation between dysregulated iron homeostasis and the presence of MetS. Systemic iron overload, although relatively mild, is frequently observed in patients with MetS.<sup>41</sup> Clinically, it presents with the hallmark features of liver iron deposition and increased levels of non-transferrin-bound iron and SF.<sup>42</sup> In the absence of traditional causes of iron overload, such as genetic hemochromatosis, chronic hemolysis, or long-term blood transfusions, patients may present with systemic iron accumulation and multiple components of MetS, a condition known as dysmetabolic iron overload syndrome (DIOS).<sup>43</sup> DIOS highlights the interaction between iron metabolism and MetS, indicating that iron metabolism disorders may be a potential factor in the pathogenesis of MetS, with a mutual influence between them.<sup>44</sup>

This study revealed a more pronounced correlation between the WWI and hyperferritinemia in female patients with T2DM, indicating the presence of sex disparities, which may be related to the fact that the WWI of female patients included in this study was significantly higher than that of male patients, and most of the participants in this study were postmenopausal women. Postmenopausal women experience alterations in hormone levels, lipid metabolism, and visceral obesity. Compared to premenopausal women and men, postmenopausal women exhibited higher levels of ROS. Increased oxidative stress may serve as a predisposing factor for the development of iron metabolism disorders in individuals who are more susceptible to such conditions.<sup>45</sup>

Finally, some limitations should be addressed in future studies. First, this was a cross-sectional study, and the observed correlation between SF levels and the WWI in individuals with T2DM does not imply causation. Second, the participants of the study were patients admitted with T2DM and a variety of complex treatment drugs, which may have introduced medication-related effects. Third, this study did not include a control group of healthy individuals, making it difficult to ascertain the correlation between SF levels and the WWI in the general population. Our study did not include inflammatory factors such as white blood cells, CRP, IL-6, etc. In future studies, we should gain a deeper understanding of the mechanism by which inflammation plays a role in disease development. Last, the dietary patterns of the study participants were not investigated, which means that the influence of diet-related factors, such as prolonged consumption of red meat, cannot be ruled out.

Consequently, a positive correlation was observed between the WWI and SF levels among patients with T2DM. These findings offer a new perspective on managing T2DM patients. For patients with higher WWI, it is essential to pay attention to their iron metabolism status and promptly implement interventions to prevent the onset of hyperferritinemia. Patients who are already experiencing hyperferritinemia, in addition to diabetes-specific treatments, should focus on weight management and fat distribution to improve iron metabolism status.

### ***Conclusion***

This study indicated a positive correlation between the WWI and SF levels among individuals with T2DM. The WWI is an independent risk factor for hyperferritinemia, especially in female patients with T2DM. In the management of type 2 diabetes, it is of utmost importance for patients to pay close attention to weight management, particularly the distribution of body fat. Simultaneously, iron metabolism should by no means be overlooked.

### **CONFLICT OF INTEREST AND FUNDING DISCLOSURE**

The authors have no relevant financial or nonfinancial interests to disclose.

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**Table 1.** Baseline characteristics according to WWI tertile grouping

Index	T1 (n = 309)	T2 (n = 269)	T3 (n = 369)	p	p for trend
Age (years)	57.17±11.08	58.14±9.90	61.71±10.33 <sup>***</sup>	<0.01	<0.01
Sex (male/female)	222/83	202/67	213/156	<0.01	0.025
Duration (years)	10.00 (4.00,15.00)	10.00 (5.00,14.50)	10.00 (5.00,15.00)	0.868	0.672
Menopause (%)	81.70%	88.10%	91.70%	0.077	0.025
Smoking (%)	24.30%	32.30%	21.70%	0.080	0.359
Drinking (%)	17.40%	20.40%	12.20%	0.016	0.054
SBP (mmHg)	139.00 (123.00,153.00)	140.00 (127.00,155.00)	142.00 (127.00,160.00) <sup>*</sup>	0.026	<0.01
DBP (mmHg)	83.00 (74.00,90.00)	85.00 (78.00,95.00) <sup>*</sup>	85.00 (74.00,95.00)	0.043	0.121
Hypertension (%)	43.60%	49.10%	56.40%	<0.01	<0.01
Weight (kg)	71.47±11.25	72.22±9.59	74.64±12.59 <sup>***</sup>	<0.01	<0.01
Hight (cm)	1.70 (1.64,1.75)	1.69 (1.63,1.75)	1.66 (1.60,1.72) <sup>***</sup>	<0.01	<0.01
BMI (kg/m <sup>2</sup> )	24.94±3.20	25.24±2.73	27.16±3.64 <sup>***</sup>	<0.01	<0.01
WC (cm)	87.21±7.35	93.96±6.36 <sup>**</sup>	99.97±8.25 <sup>***</sup>	<0.01	<0.01
HC (cm)	91.66±6.40	94.48±5.98 <sup>**</sup>	97.48±7.48 <sup>***</sup>	<0.01	<0.01
SF (ng/mL)					
Male	147.00(88.73,256.25)	228.79(138.85,335.75) <sup>**</sup>	228.79(169.85,360.00) <sup>**</sup>	<0.001	<0.01
Female	84.10(51.00,121.00)	120.00(64.90,201.00) <sup>*</sup>	172.50(116.50,228.79) <sup>***</sup>	<0.001	<0.01
Hyperferritinemia					
Male	18.5% <sup>**</sup>	27.2% <sup>**</sup>	37.3% <sup>***</sup>	<0.001	<0.01
Female	16.9%	27.2%	57.7% <sup>**</sup>	<0.001	<0.01
HbA1c (%)	7.90 (6.60,9.30)	8.40 (7.00,9.80)	8.40 (7.00,9.95) <sup>*</sup>	0.034	0.018
FPG (mmol/L)	8.23 (6.36,10.28)	8.34(6.73,11.43)	8.45(6.65,10.55)	0.240	0.171
HOMA-IR	1.86 (1.20,3.29)	2.33 (1.41,3.83) <sup>*</sup>	2.34 (1.44,4.04) <sup>**</sup>	<0.01	<0.01
FCP (ng/mL)	1.20 (0.84,1.55)	1.29 (0.97,1.63) <sup>*</sup>	1.34 (0.93,1.72) <sup>**</sup>	<0.01	<0.01
FINS (mU/L)	5.82 (3.73,8.70)	6.60(4.21,8.66)	6.88 (4.27,10.16) <sup>*</sup>	0.027	<0.01
TC (mmol/L)	4.13±1.06	4.28±1.03	4.18±1.01	0.220	0.557
TG (mmol/L)	1.43 (1.02,2.23)	1.69 (1.18,2.41) <sup>*</sup>	1.63 (1.20,2.27) <sup>*</sup>	0.010	0.012
HDL-C (mmol/L)	1.01 (0.89,1.17)	0.98 (0.85,1.12)	0.94 (0.82,1.13) <sup>**</sup>	<0.001	<0.01
LDL-C (mmol/L)	2.69 (2.14,3.19)	2.81 (2.35,3.39)	2.91 (2.32,3.48) <sup>**</sup>	<0.01	<0.01
SFA (cm <sup>2</sup> )	171.00 (134.00,210.50)	179.00 (150.00,218.50)	184.00 (141.00,229.00) <sup>*</sup>	0.018	<0.01
VFA (cm <sup>2</sup> )	111.00 (81.50,149.50)	119.00 (90.50,147.50)	124.00 (94.00,158.50) <sup>**</sup>	0.012	<0.01
NAFLD (%)	33.10%	46.80%	46.10%	<0.01	<0.01

BMI: body mass index; WC: waist circumference; HC: hip circumference; SF: serum ferritin; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; FPG: fasting glucose; HOMA-IR: insulin resistance index; FINS: fasting insulin; FCP: fasting C-peptide; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SFA: subcutaneous fat area; VFA: visceral fat area; NAFLD: nonalcoholic fatty liver disease. <sup>\*\*</sup>p < 0.01 signifies a comparison with group T1, while

<sup>\*</sup>p < 0.05 indicates a comparison with group T1

<sup>##</sup>p < 0.01 signifies a comparison with group T2

<sup>#</sup>p < 0.05 indicates a comparison with group T2

**Table 2.** Correlation analysis of the WWI and other clinical indices

INDEX	R	p
Age (years)	0.204	<0.001
Sex (male/female)	-.0172	<0.001
Duration (years)	0.026	0.430
Menopause (%)	0.140	0.015
Smoking (%)	-0.037	0.259
Drinking (%)	-0.059	0.068
Hypertension (%)	0.093	0.004
Weight (kg)	0.055	0.093
Hight (cm)	-0.235	<0.001
BMI (kg/m <sup>2</sup> )	0.268	<0.001
WC (cm)	0.614	<0.001
HC (cm)	0.335	<0.001
SBP (mmHg)	0.075	0.022
DBP (mmHg)	0.024	0.457
SF (ng/mL)	0.263	<0.001
HbA1c (%)	0.073	0.024
FPG (mmol/L)	0.054	0.099
HOMA-IR	0.114	<0.001
FCP (ng/ml)	0.091	0.005
FINS (mU/L)	0.082	0.012
TC (mmol/L)	0.021	0.515
TG (mmol/L)	0.087	0.007
HDL-C (mmol/L)	-0.106	0.001
LDL-C (mmol/L)	0.114	<0.001
SFA (cm <sup>2</sup> )	0.078	0.016
VFA (cm <sup>2</sup> )	0.083	0.011
NAFLD (%)	0.099	0.002

BMI: body mass index; WC: waist circumference; HC: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; SF: serum ferritin; HbA1c: glycated hemoglobin; FPG: fasting glucose; HOMA-IR: insulin resistance index; FCP: fasting C-peptide; FINS: fasting insulin; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SFA: subcutaneous fat area; VFA: visceral fat area; NAFLD: nonalcoholic fatty liver disease.

**Table 3.** Multiple linear regression analysis of the relationships between the WWI and SF levels

WWI group	$\beta$	t	p	95% CI	p for trend
Model 1					
T1	0 <sup>a</sup>				
T2	0.147	4.124	<0.001	(18.324, 51.604)	
T3	0.221	5.897	<0.001	(61.651, 123.151)	<0.001
Model 2					
T1	0 <sup>a</sup>				
T2	0.132	3.732	<0.001	(14.912, 47.990)	
T3	0.199	5.312	<0.001	(52.329, 113.652)	<0.001
Model 3					
T1	0 <sup>a</sup>				
T2	0.126	3.590	<0.001	(13.642, 46.543)	
T3	0.194	5.112	<0.001	(49.914, 112.12)	<0.001

a: T1 as the reference group

In linear regression analysis,  $\beta$  represents standardized regression coefficients, t refers to test statistics, and CI indicates the confidence interval.

Model 1: Adjusted for age, sex, duration of diabetes, BMI, SBP, and DBP; Model 2: Adjusted for Model 1 + HbA1c, HOMA-IR, FCP, Fins; Model 3: Model 2 + TG, HDL-C, LDL-C, VFA, SFA.

**Table 4.** Binary logistic regression analysis of the association between hyperferritinemia and the WWI

	Male			Female		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
<b>Model 1</b>						
WWI	2.209	(1,538, 3.172)	<0.001	3.485	(2.210, 5.497)	<0.001
Age	0.955	(0,937, 0.974)	<0.001	0.999	(0.971, 1.028)	0.953
Duration	0.992	(0,962, 1.022)	0.588	0.966	(0.928, 1.005)	0.087
BMI	1.037	(0,977, 1.100)	0.229	0.953	(0.886, 1.024)	0.191
Hypertension	0.758	(0,510, 1.126)	0.170	0.946	(0.560, 1.600)	0.837
<b>Model 2</b>						
WWI	2.137	(1,478, 3.090)	<0.001	3.425	(2.158, 5.438)	<0.001
Age	0.960	(0,942, 0.979)	<0.001	0.998	(0.969, 1.028)	0.907
Duration	0.995	(0,964, 1.027)	0.753	0.977	(0.936, 1.020)	0.297
BMI	1.028	(0,964, 1.096)	0.402	0.950	(0.877, 1.029)	0.209
Hypertension	0.743	(0,496, 1.114)	0.150	0.966	(0.566, 1.650)	0.899
HbA1c	1.139	(1,041, 1.245)	0.004	1.202	(1.054, 1.371)	0.006
HOMA-IR	0.920	(0,793, 1.066)	0.267	0.876	(0.716, 1.071)	0.195
Fins	1.046	(0,974, 1.123)	0.216	1.023	(0.932, 1.123)	0.629
FCP	1.186	(0,860, 1.635)	0.299	1.189	(0.767, 1.842)	0.439
<b>Model 3</b>						
WWI	2.091	(1,432, 3.054)	<0.001	3.248	(2.027, 5.204)	<0.001
Age	0.965	(0,945, 0.984)	<0.001	0.995	(0.964, 1.026)	0.731
Duration	0.997	(0,965, 1.030)	0.855	0.978	(0.937, 1.022)	0.324
BMI	1.056	(0,963, 1.157)	0.245	0.979	(0.876, 1.095)	0.709
Hypertension	0.771	(0,512, 1.161)	0.214	0.962	(0.559, 1.658)	0.89
HbA1c	1.134	(1,035, 1.242)	0.007	1.211	(1.055, 1.390)	0.006
HOMA-IR	0.906	(0,780, 1.052)	0.195	0.880	(0.715, 1.084)	0.23
Fins	1.050	(0,977, 1.129)	0.182	1.016	(0.923, 1.119)	0.745
FCP	1.121	(0,795, 1.579)	0.515	1.342	(0.852, 2.113)	0.204
TG	1.103	(1,002, 1.214)	0.046	0.816	(0.650, 1.025)	0.081
HDL	0.392	(0,144, 1.071)	0.068	0.369	(0.123, 1.109)	0.076
LDL	1.000	(0,985, 1.015)	0.989	1.341	(0.947, 1.898)	0.098
SFA	0.996	(0,991, 1.002)	0.203	0.996	(0.991, 1.001)	0.099
VFA	1.000	(0,995, 1.005)	0.958	1.002	(0.995, 1.009)	0.511

Model 1: adjusted for age, duration, BMI, hypertension (0 = no, 1 = yes); Model 2: Model 1 + HbA1c, Fins, FCP, HOMA-IR; Model 3: Model 2 + TG, HDL-C, LDL-C, SFA, VFA.

Figure 1. Comparison of glucose and lipid metabolism indicators between the hyperferritinemia and non-hyperferritinemia groups. HbA1c: glycated hemoglobin; HOMA-IR: insulin resistance index; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol. \*\* represents  $p < 0.01$ , \* represents  $p < 0.05$