


RESEARCH ARTICLE

Six-year follow-up study on the association between white blood cell count and fasting blood glucose level in Chinese adults: A community-based health examination survey

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Abstract

Background: Pre-diabetes is considered to be an important reversible stage of type 2 diabetes (T2DM); thus, early identification of pre-diabetes may help in the prevention of T2DM. This study aimed to explore the relationship between white blood cell (WBC) counts and the cumulative risk of impaired fasting glucose (IFG) regulation at 6 years.

Methods: A community-based health examination survey was conducted among individuals who were randomly selected from 1300 residents living in China in 2010 to 2016. The participants were divided into four groups according to WBC baseline level. This study initially conducted a cross-sectional analysis of the population who underwent physical examination to explore the relationship between WBC count and FBG levels. Then, a follow-up study was conducted on the population who underwent IFG normal physical examination to explore the relationship between baseline WBC count and changes in FBG levels and the cumulative risk of 6-year IFG.

Results: During the 6-year cohort follow-up, 17.2% of the participants developed IFG, and the cumulative incidence rates of IFG in the four groups were 14.7%, 16.3%, 15.8%, and 22.2%. By Cox multiple regression equation the hazard ratio (HR) of the IFG increased by 18.7% for each additional unit of baseline WBC count with no adjustment of any factor. After adjusting factors, HR increased by 8.4%.

Conclusion: Increased WBC counts are associated with risk of IFG, suggesting chronic inflammation may be involved in the development and progression of IFG.

KEYWORDS

fasting blood glucose, impaired fasting blood glucose regulation, risk, white blood cell count

1 | INTRODUCTION

Prediabetes is a glucose homeostasis disease characterized by impaired glucose tolerance or impaired fasting glucose (IFG), which is considered

to be an important reversible stage of type 2 diabetes (T2DM); thus, early identification of prediabetes may help in the prevention of T2DM.¹

Insulin resistance (IR) is a major defect in the initiation and progression of T2DM. Recently, IR has been shown to be associated with chronic low-grade inflammatory conditions.^{2,3}

Xiu Zang, Xiangyu Meng, and Yun Wang contributed equally to this work.

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Family history of diabetes, age, obesity, smoking, alcoholism, hypertension, and hyperlipidaemia have been confirmed as important predictors of T2DM.⁴ In recent years, many researches have proposed markers of low-grade inflammatory can be used as an early predictor of T2DM.^{5,6}

As one of the markers of low-grade inflammatory, white blood cell (WBC) is widely used in the evaluation of inflammation and metabolic related diseases because of its ease of monitoring and identification.⁷⁻⁹

Recently, studies have shown WBC counts as an independent risk marker for IR, diabetes, metabolic syndrome (MetS), or coronary artery disease (CAD).¹⁰⁻¹²

Especially for over a decade, cross-sectional studies have been showing that there is a close relationship between WBC and the prevalence of IFG or T2DM.¹³⁻²²

But only a few follow-up studies on the risk of WBC and IFG or T2DM count have been conducted, such as Nakanishi et al. Study showed high-level WBC can predict the progression of IFG or T2DM, especially in nonsmokers followed for 7 years.⁴ However, the follow-up population is Japanese office workers male, which is not suitable for the Chinese community. At the same time, there is a certain limitation in not considering the female group when discussing this association. Other prospective studies have also shown a close relationship between WBC and the prevalence of IFG or T2DM.^{23,24} However, these studies usually involve relatively few subjects, and the subjects are not representative. Our study included men and women between the ages of 20 and 70, while Tanigawa et al included only middle-aged men.²⁵

Therefore, we used a prospective correlation study design to observe the incidence of IFG at different WBC counts during follow-up, further determine the impact of WBC on IFG, and further identify the risk indicators for predicting prediabetes.

In summary, this study initially conducted a cross-sectional analysis of the population who underwent physical examination to explore the relationship between WBC count and fasting blood glucose (FBG) levels. Then, a follow-up study was conducted on the population that underwent IFG normal physical examination to explore the relationship between baseline WBC count and changes in FBG levels and the cumulative risk of 6-year IFG.

2 | PATIENTS AND METHODS

2.1 | Patients

A total of 1300 patients (aged 20-70 y) were enrolled. All patients underwent physical examination at Xuzhou Central Hospital from 2010 to 2016. Patients with the following physiological and pathological conditions that caused leukocytosis were excluded from the study²⁶:

1. those with acute and chronic infectious diseases, including upper respiratory infections, parasitic infections, and inflammations of various systems;
2. those who had tissue damage, including burns, trauma, and after major surgery;
3. those who were bleeding caused by various reasons, causing tissue concentration, and resulting in increased WBC count;

4. those with severe primary disease in the biliary system, pancreas, heart, brain, kidney, and haematopoietic system as well as diabetes;
5. those with psychiatric disorders who were unable to communicate with their doctors or who have incomplete information;
6. those with history of drug use and food allergy;
7. those with autoimmune diseases;
8. those who received inhalation/oral corticosteroid therapy or developed other lung diseases; and
9. those who received antiinhibitory or cytotoxic drugs within 1 year.

Finally, a total of 1095 patients were enrolled and analysed. All patients provided informed consent for participation. The study was reviewed and approved by the ethics committee of the Central Hospital of Xuzhou.

3 | METHODS

3.1 | Data collection

Measurement of height, weight, and blood pressure (BP) was conducted by professional staff.

Height and weight were measured in patients wearing light clothing and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. BP was measured by trained doctors using a mercury sphygmomanometer on the dominant arm after a resting period of at least 5 minutes in the supine position. The patient's arm was placed at the heart level, and BP values were taken as the mean of three measurements.

3.2 | Questionnaire survey

The general condition, sex, age, past history, family history, alcohol and tobacco hobbies, and medications in the past 6 months were obtained by qualified physicians and researchers and were recorded on the unified design form. All staff were intensively trained to standardize operational procedures and methods prior to the study. Questionnaires were used to obtain the demographic data (sex, age, etc), past medical history (cardiovascular disease, hypertension, diabetes, etc), as well as smoking status, drinking status, income status, and education level.

3.3 | Assessment of biomarkers and covariates

The following biomarkers were measured in all participants: WBC, red blood cell (RBC), haemoglobin (Hgb), platelet (PLT), FBG, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total protein (TP), serum creatinine, serum uric acid (SUA), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). A venous blood sample was drawn from all patients after an overnight fast (at least 10 h) and allowed to clot at room temperature for 1 to 3 hours. Immediately after clotting, the serum was separated by centrifugation for 15 minutes at 3000 rpm (centrifugal radius one-fourth 11 cm). All biochemical assays were determined enzymatically using an autoanalyser (Type 7600, Hitachi Ltd, Tokyo, Japan).

3.4 | Statistical analysis

Data management and statistical analysis were performed using SPSS version 17.0. All hypothesis tests were performed using a two-tailed test. Measured data were expressed as means \pm standard deviation ($\bar{x} \pm s$), and count data were expressed as numerical values. The patients were divided into four groups according to their WBC count by sex (in quintiles). Differences in continuous variables at baseline were tested using one-way analysis of variance. General linear models were used to compare geometric mean values of quantitative traits, while chi-squared tests were used to compare the proportion of categorical variables across groups. We used survival analysis and cox regression analysis to estimate the hazard ratios (HRs) for IFG risk, adjusting for the covariates age, sex, BMI, and biomarkers. We used restricted cubic spline regressions to continuously model the association between WBC count and the risk for IFG. A *P* value of less than or equal to 0.05 was considered significant.

4 | RESULTS

4.1 | Baseline characteristic of patients

A total of 1095 patients with no FBG impairment were recruited in this study, while six of whom were lost because of phone number changes. According to the WBC baseline level, male and female participants were divided into four groups, respectively. (female:

Q1 < 4.722, 4.722 \leq Q2 < 5.445, 5.445 \leq Q3 < 6.39, Q4 \geq 6.39; male: Q1 < 5.412, 5.412 \leq Q2 < 6.42, 6.42 \leq Q3 < 7.51, Q4 \geq 7.51). Q1 comprised 274 patients; Q2, 275 patients; Q3, 273 patients; and Q4, 273 patients. Table 1 shows that RBC, Hgb, PLT, TP, SUA, TC, TG, LDL, BMI, smoking, and drinking were increased as the WBC increased, whereas HDL decreased as the WBC increased (*P* < 0.05).

4.2 | Cumulative incidence of IFG in different categories of percent WBC during the follow-up period

During the 6-year follow-up, 188 IFG patients out of 1095 participants were identified (Table 2). The cumulative incidence of IFG was 17.2%. In the sixth year, the cumulative incidence of IFG in four groups were 14.7%, 16.3%, 15.8%, and 22.2%, respectively (Figure 1), and the trend was considered significant (*P* = 0.032) (Table 2).

4.3 | Association between baseline WBC and risk of IFG

Moreover, we assessed the association between baseline WBC and risk of IFG by Cox multiple regression equation (Table 3). In model 1, in cases where risk factors were unadjusted, the baseline WBC increased one unit as the HR of IFG increased to 18.7% (HR = 1.187; 95% confidence interval [CI], 1.104-1.593). After adjusting for sex,

TABLE 1 Baseline characteristic of patients by quartile of white blood cell count

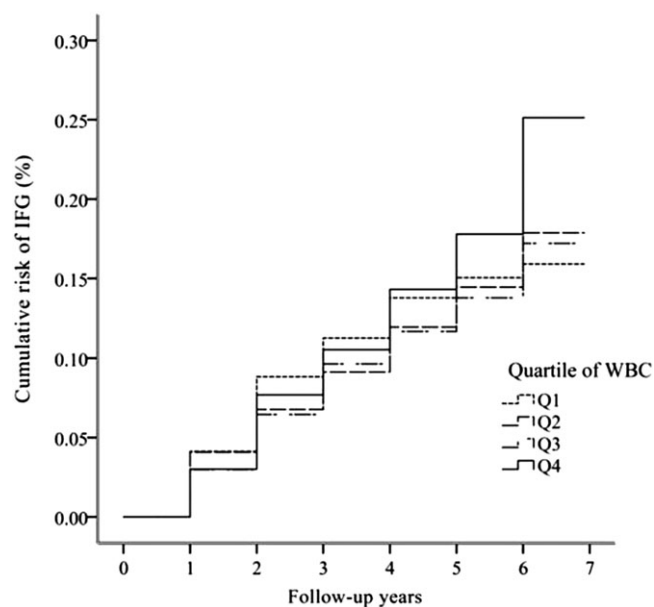
	White Blood Cell ($10^9/L$)				P for trend
	Q1	Q2	Q3	Q4	
n	274	275	273	273	
Male	109	111	108	108	
Age, years	47.83 \pm 10.38	47.67 \pm 10.42	47.94 \pm 10.99	46.48 \pm 9.74	0.327
RBC, $10^9/L$	4.56 \pm 0.46	4.63 \pm 0.45	4.71 \pm 0.43	4.73 \pm 0.41	<0.001
HGb, g/L	134.55 \pm 17.07	136.78 \pm 15.21	139.03 \pm 14.02	140.17 \pm 13.06	<0.001
PLT, $10^9/L$	196.08 \pm 44.25	205.98 \pm 38.92	216.74 \pm 43.91	225.77 \pm 42.53	<0.001
ALT, U/L	17.54 \pm 10.63	21.32 \pm 39.39	19.82 \pm 11.08	20.64 \pm 12.83	0.211
AST, U/L	17.55 \pm 5.06	19.60 \pm 19.33	18.26 \pm 5.42	18.19 \pm 6.94	0.165
TP, g/L	75.02 \pm 4.33	75.41 \pm 3.93	75.89 \pm 4.15	76.04 \pm 4.59	0.02
Scr, $\mu\text{mol/L}$	61.35 \pm 13.87	60.18 \pm 12.67	61.05 \pm 12.34	60.07 \pm 12.46	0.573
SUA, $\mu\text{mol/L}$	286.94 \pm 80.06	298.27 \pm 82.90	305.54 \pm 78.90	306.45 \pm 73.35	0.015
TC, mmol/L	4.73 \pm 0.88	4.87 \pm 0.82	4.93 \pm 0.89	4.95 \pm 0.89	0.014
TG, mmol/L	1.24 \pm 0.83	1.46 \pm 1.42	1.55 \pm 1.49	1.82 \pm 1.64	<0.001
HDL, mmol/L	1.59 \pm 0.39	1.51 \pm 0.37	1.50 \pm 0.34	1.42 \pm 0.36	<0.001
LDL, mmol/L	2.85 \pm 0.69	2.97 \pm 0.71	3.01 \pm 0.78	3.04 \pm 0.76	0.013
BMI, kg/m ²	23.14 \pm 3.08	23.77 \pm 2.89	23.94 \pm 3.01	24.53 \pm 3.51	<0.001
SBP, mmHg	122.47 \pm 16.21	122.84 \pm 15.98	123.35 \pm 16.24	124.62 \pm 17.69	0.455
DBP, mmHg	77.53 \pm 10.51	78.13 \pm 10.01	78.50 \pm 9.99	79.52 \pm 11.18	0.16
FPG, mmol/L	5.15 \pm 0.39	5.15 \pm 0.41	5.14 \pm 0.39	5.16 \pm 0.42	0.902
Smoking	30	33	42	51	0.005
Drinking	62	64	77	89	0.004

Abbreviations: ALT, glutamic pyruvate; AST, glutamic transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting blood glucose; Hgb, haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PLT, platelet; RBC, red blood cell; SBP, systolic pressure; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; TP, total protein.

TABLE 2 The number of patients with prediabetes in four categories of percent white blood cell (WBC) during the follow-up period

		White Blood Cell, 10 ⁹ /L				χ^2	P for trend
		Q1	Q2	Q3	Q4		
1-year follow-up	IFG	11	11	8	8	0.747	0.387
	Normal	263	264	264	265		
2-year follow-up	IFG	23	18	17	20	0.242	0.622
	Normal	250	257	255	252		
3-year follow-up	IFG	29	24	25	28	0.036	0.849
	Normal	244	251	247	244		
4-year follow-up	IFG	35	31	30	36	0.017	0.898
	Normal	237	244	242	234		
5-year follow-up	IFG	38	37	35	44	0.453	0.68
	Normal	234	238	237	226		
6-year follow-up	IFG	40	45	43	60	4.573	0.032
	Normal	232	230	229	210		

Abbreviations: IFG: impaired fasting glucose; WBC: white blood cell.

**FIGURE 1** The cumulative incidence of IFG of four categories of percent WBC during follow-up period (IFG: impaired fasting glucose; WBC: white blood cell count)**TABLE 3** Association between baseline white blood cell (WBC) and risk of impaired fasting glucose (IFG)

	Beta	Wald	P	HR	95% CI
Model 1	0.228	6.015	0.002	1.187	1.104-1.593
Model 2	0.141	4.474	0.034	1.151	1.010-1.311
Model 3	0.086	4.014	0.042	1.084	1.001-1.304

Abbreviations: HR: hazard ratio; IFG: impaired fasting glucose; WBC: white blood cell.

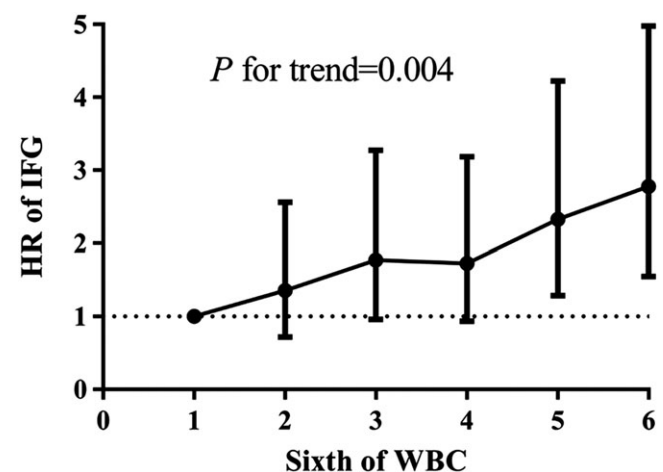
Model 1: unadjusted; model 2: adjusted for sex, age, and body mass index (BMI); model 3: adjusted for sex, age, BMI, systolic pressure (SBP), diastolic blood pressure (DBP), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum uric acid (SUA), smoking, and drinking.

age, and BMI, the HR also increased (HR = 1.151; 95% CI, 1.010-1.311). In model 3, after adjusting for sex, age, BMI, SBP, DBP, TG, TC, HDL, LDL, SUA, smoking, and drinking, the baseline WBC increase one unit as the HR increased to 8.4% (HR = 1.084; 95% CI, 1.001-1.304).

Figure 2 shows that during the 6-year follow-up, as the baseline WBC count increased, the HR of IFG also increased year by year. The trend of increase was significant ($P = 0.004$). The HR of IFG in the sixth year was doubled compared with that in the first year. Studies have reported that BMI levels were associated with increased risk of IFG, metabolic syndrome, type 2 diabetes, etc.²⁷ So, by stratifying the effects of BMI on WBC and IFG, we found significant interactions between WBC and BMI in relation to IFG risk. As a result, obese people with high WBC baseline levels are at significantly higher risk of developing IFG than those with low WBC baseline in non-obese people, with increased follow-up, as presented in Supplement Table 1 and Supplement Table 2 (supplementary material online).

5 | DISCUSSION

This study found that as the number of follow-up years increased, the risk of IFG increased with increasing baseline WBC. This finding is consistent with those reported in previous studies conducted in Asian Indians²⁸ and Japanese.⁴ In addition, we found that this association persisted after adjusting for risk factors known for possible changes in glucose status (age, obesity, history of hypertension, family history of diabetes, history of dyslipidaemia, and smoking, drinking. These

**FIGURE 2** The trend of HR with sixth of baseline WBC (HR: hazard ratio; IFG: impaired fasting glucose; WBC: white blood cells count)

results indicate that elevated WBC count is an independent risk factor for IFG risk.

Through multiple linear regression analysis, we also found that TC, TG, LDL, and BMI increased with the increase of WBC, and HDL decreased with the increase of WBC ($P < 0.05$). The results show that high BMI and dyslipidaemia have important adverse effects on WBC. Our results are consistent with those reported in previous large prospective cohort studies.^{29,30} These previous studies have found that obesity can lead to low-grade chronic inflammation in the body, which resulted in the development of metabolic disorders and complications.⁷

Finally, the relationship between elevated WBC count and hypertension reported in previous studies^{31,32} was not observed in this study.

Although the association between WBC and IFG regulation is still unclear, we suspect that IR may be part of the cause. Defects in the action of insulin on major insulin-sensitive tissues (adipose tissue, muscle, and liver) led to chronic low-grade inflammatory states and activated various proinflammatory factors such as interleukin-1, interleukin-6, tumour necrosis factor alpha, monocyte chemotactic protein, leptin, and resistin, which promote the differentiation of WBC, accelerate the maturation of WBC, and inhibit the migration of inflammatory factors to the extravascular, thus causing an increase in circulating WBC and leading to an increase in peripheral blood inflammatory factors.^{33,34} Second, the inflammation itself can impair insulin signalling² and promote beta cell death.³⁵ Thus, the relationship between IR and WBC count as a marker of inflammation is bidirectional: IR and insulin sensitivity deficiency led to the release of chronic inflammation and inflammatory markers. By contrast, chronic inflammation will promote IR.³⁶

Previous evidence has shown that WBC counts may be a predictor of diabetes risk, and our findings are consistent with those reported in previous studies. However, most previous studies have been based on WBC counts and IR cross-sectional studies. Therefore, our results demonstrate that dynamic changes in WBC counts may play an important role in the development of diabetes or prediabetes. At the same time, high levels of long-term WBC increase the risk of IFG regulation, thus further increasing the risk of diabetes. Therefore, this study aimed to predict the HR of IFG and assist practitioners in the early identification of prediabetes and diabetes and the early adjustment of lifestyle by detecting WBC counts to reduce the social burden of prediabetes, diabetes, and its complications.

This study had several limitations. First, the study sample consisted of urban workers and residents, all of whom were selected from the population who underwent routine physical examination, and the source is more limited. Second, this study did not analyse the relationship between leukocyte subpopulation, such as neutrophils and lymphocytes and IFG risk. Therefore, further studies must establish the predictive value of WBC and leukocyte subpopulation for IFG risk and islet function. Finally, although many possible confounding variables have been adjusted in the risk analysis, including age, smoking, drinking, blood pressure, and other laboratory measurements, other potential confounders, such as lifestyle differences, drug history, and comorbidities, cannot be properly adjusted because the baseline data obtained through the questionnaire were incomplete. The existence of these problems may have an impact on the results.

In summary, we found that in the Chinese population, even if the WBC count is within the normal range, increase in circulating WBC count is positively correlated with the risk of IFG regulation. Therefore, our study concluded that the elevation of WBC counts may indicate a higher risk of developing IFG and T2DM. Finally, combined with the results of our study, we know that WBC count is also related to BMI, smoking, TGs, LDL levels, HDL levels. Therefore, weight control, early smoking cessation, and lipid-lowering treatments are needed to improve chronic low-grade inflammation. It can also help prevent pre-diabetes and T2DM by detecting WBC counts.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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