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ORIGINAL RESEARCH

White Blood Cell Count as a Predictor of Incident Type 2 Diabetes Mellitus Among Non-Obese Adults: A Longitudinal 10-Year Analysis of the Korean Genome and Epidemiology Study

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Purpose: Limited evidence is available on whether the white blood cell (WBC) count is a predictor of type 2 diabetes mellitus (T2DM) in non-obese individuals. This study aimed to determine whether WBC count could be used as an indicator for the prediction of incident T2DM among non-obese individuals using a large, community-based Korean cohort that was observed over 10 years.

Patients and methods: A total of 4211 non-obese adults without diabetes aged 40–69 years were selected from the Korean Genome and Epidemiology Study. The participants were divided into four groups according to WBC count quartiles. We prospectively assessed the hazard ratios (HRs) with 95% confidence intervals (CIs) for incident T2DM, based on the American Diabetes Association criteria, using multivariate Cox proportional hazards regression models over 10 years after the baseline survey.

Results: During the follow-up period, 592 (14.1%) participants had newly developed T2DM. The higher quartile of WBC count groups showed significantly higher cumulative T2DM incidence over 10 years after the baseline survey (log-rank test, P < 0.001). Compared with the HRs for individuals in the referent lowest quartile, the HR (95% CI) for incident T2DM in individuals in the highest quartile was 1.55 (1.10–2.18) after adjusting for confounding variables.

Conclusion: A higher WBC count predicts future incident T2DM among community-dwelling non-obese Korean adults. This study suggests that WBC count could facilitate the prediction of non-obese individuals susceptible to T2DM.

Keywords: white blood cell count, type 2 diabetes mellitus, chronic low-grade inflammation, non-obese adults

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by relative insulin deficiency caused by insulin resistance in target organs and pancreatic β-cell dysfunction.[1] Worldwide, it is a challenging public health problem because of its high prevalence and concomitant risks of various complications, and it is a major leading cause of disability and death in adults globally.[2,3] In addition, individuals with T2DM, on an average, have approximately 2.3 times higher medical expenditures than those without T2DM.[4] The global prevalence of T2DM increased from 4.7% in 1980 to 9.3% in 2019, and is estimated to rise to 10.2% (578 million) by 2030.[5,6] Similarly, in South Korea, the prevalence of

T2DM has rapidly increased during the past several decades from 8.6% in 2001 to 14.4% in 2016.[7,8] Furthermore, T2DM was the sixth leading cause of death in South Korea in 2018.[9]

Although obesity has long been considered a major risk factor for T2DM, susceptibility to T2DM has been reported to have heterogeneous features according to ethnicity and cultural subgroups.[10] Specifically, Asians develop T2DM at a lower body-mass index (BMI) when compared with Caucasians, and the risk of T2DM starts at a lower BMI for Asians than for the Western populations.[11,12] Indeed, the proportion of non-obese individuals among all T2DM patients was 52.6% for men and 47.9% for women in 2013 in Korea.[8] Interestingly, the prevalence of obesity among Korean women has decreased gradually from around 2000,[13,14] whereas the incidence of T2DM has increased steadily over the last decade.[15] Thus, early identification of individuals at high risk of T2DM in non-obese adults is considered important from a public health perspective.

Insulin resistance and T2DM are closely related to chronic low-grade inflammation.[16,17] Inflammation markers, such as the white blood cell (WBC) count, high-sensitivity C-reactive protein (hsCRP), and interleukin-6, are known to be associated with metabolic syndrome and T2DM.[18–20] Furthermore, several studies have revealed that WBC count, which is commonly measured in routine laboratory examination panels, is related to insulin resistance and predicts the development of T2DM.[21–24] In particular, it was reported that WBC count could be used as an indicator for the prediction of T2DM incidence among obese individuals.[25] However, few prospective cohort studies have examined the relationship between WBC count and incident T2DM among non-obese individuals. Thus, this study aimed to determine whether WBC count could be used as an indicator for the prediction of incident T2DM among non-obese individuals using a large, community-based Korean cohort that was observed over 10 years.

Patients and Methods
Study Overview and Study Participants
Participants were recruited from the Korea Association Resource study, which is a part of the Korean Genome and Epidemiology Study (KoGES), a population-based prospective cohort study conducted by the Korean Centers for Disease Control and Prevention. Detailed information about the study participants and methodology

of KoGES has been described in a previous study.[26] In the KoGES study, adults aged 40–69 years in Ansung (a rural area) and Ansan (an urban area) were enrolled to investigate the prevalence of and risk factors for chronic diseases in Korea.

A total of 8840 adults aged 40–69 years were included in the baseline study conducted from 2001 to 2002. Baseline examinations were conducted in 2001–2002, and follow-up examinations continued biennially until 2012. Among the 8840 participants in the baseline survey, we excluded 3062 obese participants. We defined obese participants as those individuals with a BMI ≥ 25 kg/m^2 based on the Asia-Pacific regional guidelines of the World Health Organization and International Obesity Task Force.[27] We also excluded 613 participants because they either were previously diagnosed with T2DM or met the diagnostic criteria for T2DM in the baseline survey. Of the remaining participants, we also excluded 464 participants with a WBC count <4000 cells/mL or >10,000 cells/μL to rule out the possibility of an inflammatory disorder, infection, or bone marrow suppressive illness. During the 10-year follow-up period, 490 participants were further excluded due to loss to follow-up and incomplete follow-up data. After these exclusions, 4211 participants were included in the final analysis. All individuals voluntarily participated in the study, and informed consent was obtained from all participants. This study was approved by the Institutional Review Board of Yonsei University Yongin Severance Hospital (Institutional Review Board number 9–2016-0013). In addition, this study complied with the ethical principles underlined in the Declaration of Helsinki.

Clinical and Biochemical Measurement
The study data included the medical history and socio-demographic information recorded by a self-administered questionnaire, anthropometric measurements, and laboratory biochemical measurements. All study participants were also requested to answer a health-related behavior questionnaire that included topics related to smoking and alcohol consumption. In the present study, current smokers were individuals who smoked ≥ 100 cigarettes in their lifetime and currently smoked at the time of the study, and an alcohol drinker was defined as an individual who consumed alcohol more than twice a week.

Participants' body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with participants wearing light indoor clothing and no shoes. The BMI was calculated as weight (kg) divided by the square of the height

(m^2). The waist circumference was measured to the nearest 0.1 cm at the midpoint between the lower border of the rib cage and the iliac crest at the end stage of normal expiration. Systolic and diastolic blood pressures were measured twice using a standard mercury sphygmomanometer (Baumanometer Standby; W.A. Baum, New York, NY, USA).

Blood samples were obtained in the morning after an overnight fast. WBC count was determined using a hematological analyzer (ADVIA 120; Siemens, Tarrytown, NY, USA). Glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol levels were measured using an automatic analyzer (ADVIA 1650; Siemens, Tarrytown, NY, USA). Glycated hemoglobin A1c (HbA1c) levels were measured using high-performance liquid chromatography (Variant II; BioRad Laboratories, Hercules, CA, USA). Insulin levels were determined using a radioimmunoassay kit (LINCO Research, St. Charles, MO, USA) with intra-assay and inter-assay coefficients of variation ranging from 2.1% to 8.3%. The Denka Seiken (Tokyo, Japan) assay, which has been validated against the Dade Behring method, was used to measure hsCRP level. The homeostatic model assessment of insulin resistance (HOMA-IR) was determined using the following equation: fasting glucose (mg/dL) × fasting insulin (μIU/mL)/405. T2DM was defined as the presence of one or more of the following conditions: fasting glucose level ≥ 126 mg/dL, HbA1c ≥ 6.5%, and 2-hour plasma glucose level of oral glucose tolerance test ≥ 200 mg/dL, based on the American Diabetes Association,[28] or ongoing treatment with oral antidiabetic medications or insulin therapy. Prediabetes was defined as one or more of the following conditions: fasting glucose level between 100–125 mg/dL, HbA1c level between 5.7–6.4%, and 2-hour plasma glucose level between 140–199 mg/dL in the oral glucose tolerance test.

Statistical Analyses

WBC count quartiles were categorized as follows: Q1, ≤ 5200; Q2, 5300–6100; Q3, 6200–7300; and Q4, ≥ 7400 cells/μL. The baseline characteristics of the study population according to WBC count quartiles were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables according to the normality of distributions. The chi-squared test was used to compare the categorical variables. Continuous data are presented as means ± standard deviation or medians (interquartile range). Categorical data are presented as frequencies.

The hazard ratios (HRs) with 95% confidence intervals (CIs) for incident T2DM were calculated using multivariate Cox proportional hazards regression models after adjusting for potentially confounding variables. The lowest quartile, Q1, was set as the reference group for the WBC count. The cumulative incidence of T2DM was determined using the Kaplan-Meier curve. Log-rank tests were conducted to determine the differences in the cumulative incidence of T2DM among the groups. The Contal and O'Quigley method was used to determine the optimal cut-off point for the WBC count with maximized log-rank statistics.

All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). A *p*-value < 0.05 was considered as significant.

Results

Table 1 presents the baseline characteristics of 4211 participants without T2DM at baseline according to their WBC count quartiles. The mean values of a few cardiometabolic variables, such as blood pressure, triglycerides, and hsCRP levels, tended to increase proportionally with the WBC count quartiles. However, there was no significant difference in the median values of insulin and HOMA-IR among the WBC count quartiles.

Table 2 shows the incidence of T2DM during the 10-year follow-up period, during which the incidence rates were calculated biennially. A total of 592 individuals (14.1%, 592 of 4211) developed T2DM during the 10-year follow-up period. The incidence rate per 2 years ranged from 1.2–5.9.

The cumulative incidence of T2DM according to WBC count quartiles is illustrated in Figure 1 as a Kaplan–Meier curve. The higher quartile of WBC count groups showed significantly higher cumulative T2DM incidence over 10 years after the baseline survey (log-rank test, P < 0.001).

Table 3 shows the results of the multivariate Cox proportional hazards regression analysis for predicting T2DM according to WBC count quartiles. In Model 1, we calculated the hazard ratios after adjusting for age and sex. In model 2, we adjusted for additional potential confounding variables, including smoking, alcohol consumption, waist circumference, systolic blood pressure, fasting plasma glucose, and family history of T2DM. In model 3, we investigated the association between WBC count and incident T2DM by additional adjustment for HOMA-IR, hsCRP levels, and prediabetes. Compared to the reference first quartile, the HRs (95% CIs) of the incidence of T2DM in the second, third, and fourth

Table 1 Baseline Characteristics of the Study Population According to WBC Count Quartiles

	Total (n = 4211)	WBC Count Quartiles				
		Q1 (≤ 5200) (n = 1006)	Q2 (5300–6100) (n = 1067)	Q3 (6200–7300) (n = 1115)	Q4 (≥ 7400) (n = 1023)	p-value
Age (years)	52.2 ± 9.0	51.8 ± 9.0	52.3 ± 8.9	52.3 ± 9.3	52.2 ± 8.8	0.550
Sex (%)	47.8	36.6	45.5	50.4	58.4	<0.001
BMI (kg/m²)	22.4 ± 1.8	22.4 ± 1.8	22.5 ± 1.7	22.5 ± 1.8	22.5 ± 1.8	0.360
Waist circumference (cm)	79.4 ± 8.0	78.6 ± 8.1	79.3 ± 7.8	79.6 ± 7.9	80.2 ± 8.1	<0.001
Systolic blood pressure (mmHg)	119.6 ± 18.3	117.9 ± 17.4	119.4 ± 18.1	119.8 ± 18.7	121.5 ± 18.9	<0.001
Diastolic blood pressure (mmHg)	77.8 ± 10.7	77.8 ± 10.7	78.7 ± 11.3	79.4 ± 11.5	79.8 ± 11.5	<0.001
Fasting plasma glucose (mg/dL)	82.5 ± 8.7	82.2 ± 8.5	82.5 ± 8.8	82.7 ± 8.4	82.5 ± 9.2	0.545
Insulin (μIU/mL)	6.5 (4.9–8.8)	6.4 (4.8–8.4)	6.6 (4.9–8.7)	6.6 (5.0–8.8)	6.6 (4.8–9.1)	0.359
HOMA-IR	1.32 (0.98–1.80)	1.29 (0.97–1.74)	1.32 (0.98–1.80)	1.32 (1.00–1.82)	1.32 (0.96–1.85)	0.197
Total cholesterol (mg/dL)	187.5 ± 33.7	184.7 ± 32.5	187.3 ± 33.8	186.7 ± 33.2	191.3 ± 34.9	<0.001
Triglyceride (mg/dL)	124.0 (94.0–169.0)	111.0 (86.0–147.0)	122.0 (93.0–164.0)	127.0 (98.0–173.0)	138.0 (101.0–192.0)	<0.001
HDL cholesterol (mg/dL)	46.1 ± 10.3	47.1 ± 10.3	46.1 ± 9.9	45.5 ± 10.2	45.7 ± 10.9	0.002
hsCRP (mg/L)	0.12 (0.05–0.22)	0.10 (0.04–0.17)	0.12 (0.05–0.19)	0.13 (0.05–0.23)	0.15 (0.07–0.28)	<0.001
Current smoker (%)	26.2	14.9	20.9	27.0	41.8	<0.001
Alcohol drinker (%)	22.8	17.5	20.7	24.7	28.0	<0.001
Family history of diabetes (%)	9.9	9.7	10.1	10.1	9.7	0.976
Prediabetes (%)	35.9	30.1	34.1	37.4	41.9	<0.001

Notes: Data are expressed as the mean ± standard deviation, median (interquartile range), or percentage; p-values were calculated using ANOVA, the Kruskal-Wallis test, or chi-squared test.
Abbreviations: WBC, white blood cell; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table 2 Incidence of Type 2 Diabetes During the Follow-Up Study

Year Range	Follow-Up	n	Incidence of Cases (n)	Incidence Rate per 2 Years
2001–2002	Baseline	4211		
2003–2004	2 years	3973	47	1.2
2005–2006	4 years	3559	83	2.3
2007–2008	6 years	3161	109	3.5
2009–2010	8 years	3188	188	5.9
2011–2012	10 years	2994	165	5.5

quartiles increased in a dose–response manner among all models. Compared to the lowest quartiles, the HRs (95% CIs) of the incidence of T2DM in the highest WBC count quartile were 2.04 (1.48–2.81) in the unadjusted model, 1.96 (1.42–2.70) in model 1, 1.71 (1.22–2.39) in model 2, and 1.55 (1.10–2.18) in model 3.

Supplementary Figure S1 suggests the potential of a clinically meaningful WBC count threshold at ≥ 6600 cells/μL.

Discussion

In this large-scale prospective community-based Korean cohort that was observed over 10 years, we found that a higher WBC count was positively and independently associated with incident T2DM among community-dwelling non-obese Korean adults. This association between WBC count and incidence of T2DM was independent of insulin resistance, even after adjusting for HOMA-IR. Our findings are consistent with the results of previous studies showing that an increased WBC count is positively associated with incident T2DM.[21–24] Moreover, our results suggest that WBC count could be a useful marker for non-obese adults susceptible to T2DM, independent of insulin resistance. Few previous studies have examined the relationship between WBC count and the incidence of T2DM among non-obese adults. We believe that this is the first large population-based cohort study to reveal a positive relationship between WBC count and the incidence of T2DM regardless of baseline insulin resistance in a non-obese population. Thus, our results expand upon earlier findings regarding the association between WBC count and incident T2DM. Smoking, waist circumference, and hsCRP levels tended to increase with WBC count quartiles, and they could influence the relationship between WBC count and incident T2DM. We included these factors as confounding variables in Cox regression analyses to control for potential confounding. An interaction test was also performed, and it identified that the influence of the WBC count is not dependent on
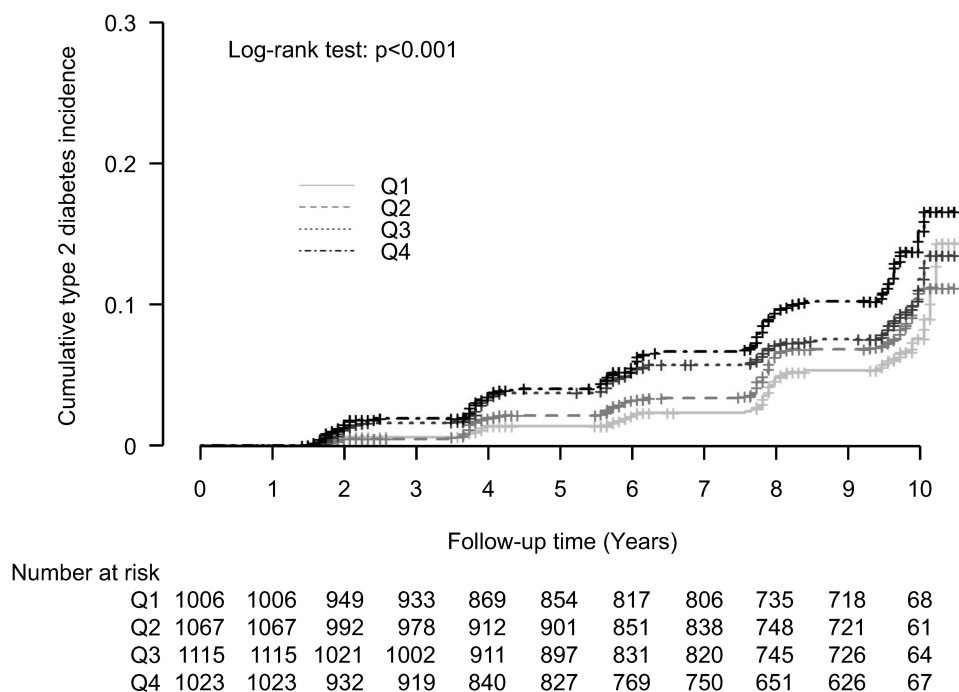

Number at risk											
Q1	1006	1006	949	933	869	854	817	806	735	718	68
Q2	1067	1067	992	978	912	901	851	838	748	721	61
Q3	1115	1115	1021	1002	911	897	831	820	745	726	64
Q4	1023	1023	932	919	840	827	769	750	651	626	67

Figure 1 Cumulative incidence of type 2 diabetes according to WBC count quartiles in the non-obese population.

Table 3 Hazard Ratios and 95% Confidence Intervals for Incident Type 2 Diabetes According to WBC Count Quartiles

	WBC Count Quartiles			
	Q1 (≤ 5200) (n = 1006)	Q2 (5300–6100) (n = 1067)	Q3 (6200–7300) (n = 1115)	Q4 (≥ 7400) (n = 1023)
New cases of diabetes, n	58	75	87	108
Mean follow-up, years	8.41	8.25	7.99	7.92
Person-years of follow-up	8463	8807	8905	8098
Unadjusted	1.00	1.28 (0.91–1.80)	1.48 (1.06–2.06)	2.04 (1.48–2.81)
Model 1	1.00	1.23 (0.87–1.73)	1.42 (1.02–1.98)	1.96 (1.42–2.70)
Model 2	1.00	1.27 (0.90–1.80)	1.45 (1.03–2.03)	1.71 (1.22–2.39)
Model 3	1.00	1.22 (0.96–1.72)	1.39 (0.99–1.95)	1.55 (1.10–2.18)

Notes: Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking, alcohol consumption, waist circumference, systolic blood pressure, fasting plasma glucose, and family history of type 2 diabetes. Model 3: adjusted for age, sex, smoking, alcohol consumption, waist circumference, systolic blood pressure, fasting plasma glucose, family history of type 2 diabetes, HOMA-IR, hsCRP, and prediabetes.
Abbreviations: WBC, white blood cell; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

each variable. Further studies are warranted to elucidate the relationship between WBC count and incident T2DM among non-obese adults by matching these factors, or subgroup analysis, in more participants.

Chronic low-grade inflammation is known to be involved in the pathogenesis of obesity-related T2DM.[16,29] Adipose tissue is generally considered as the major and earliest trigger of chronic low-grade inflammation in obesity-related T2DM, with prominent infiltration of lymphocytes, macrophages, and other immune cells into this tissue.[30–33] These cells are essential for the production of pro-inflammatory cytokines, which function in an autocrine and paracrine fashion to induce insulin resistance by inhibiting insulin signaling in peripheral tissues.[34–36]

Non-obese individuals with T2DM were also identified by an increase in pro-inflammatory cytokines, such as interleukin-8 and interleukin-18.[37] Unlike obesity-related T2DM, dysfunctional adipocytes could not be considered as the major determinants of chronic low-grade inflammation, and over-nutrition could not be regarded as the only trigger of chronic low-grade inflammation in the case of non-obese individuals with T2DM. Other factors, such as pancreatic β-cell failure and alterations in gut microbiota composition, are also possible mechanisms of inflammation that are involved and can also be found in non-obese T2DM. It has been suggested that the "stressed" pancreatic β-cell may trigger local inflammation and alter the balance between pancreatic β-cell mass and function in

Langerhans islets in individuals with a genetic predisposition, which leads to a decrease in both pancreatic β-cell number and function.[38–41] Macrophages, interleukin-1β, and other immune cells are known to be involved in islet inflammation in T2DM.[42–44] In addition, altered gut microbiota can directly influence immune cells in the gut and indirectly influence immune cells through microbial products, such as short-chain fatty acids, lipopolysaccharides, and other metabolites, all of which can have an effect on insulin resistance.[45–48] Short-chain fatty acids are believed to regulate gene expression of human monocytes and decrease chemokine production and inflammatory cytokine, whereas lipopolysaccharides can lead to subclinical inflammation mediated by the induction of pro-inflammatory cytokines by immune cells.[45,49]

This study has several limitations that should be considered. First, only one measurement of WBC count was included in the analysis, and thus, it was not possible to determine whether an acute and brief episode of infection affected the findings observed in this study. In an attempt to minimize this limitation, participants with a WBC count ≥ 10,000 cells/mL were excluded. Second, this study did not show the effect of sequential changes in the WBC count, since we only considered the baseline measurements of the WBC count. Third, the KoGES did not duplicate the measurement of blood glucose levels, and T2DM diagnosis could not be confirmed by repeat testing. Fourth, this study did not exclude the presence of potential

autoimmune or inflammatory disorders. Therefore, further studies that consider latent autoimmune diabetes in adults, autoimmune diseases, and inflammatory diseases are needed. Fifth, despite the large population size, this study was performed in a Korean population. Therefore, our results may not be generalizable to other racial/ethnic populations. Lastly, the study population may not represent the general Korean population, since the participants resided in a rural area and an urban area. Therefore, this study may have been subject to a selection bias. Despite these limitations, we believe that our findings would have clinical implications with regard to preventive public health strategies among non-obese individuals who may be at a high risk of developing T2DM.

Conclusion

In conclusion, a higher WBC count predicts future incident T2DM that is independent of other associated variables, including HOMA-IR, among community-dwelling non-obese Korean adults. In clinical practice, WBC count, which is inexpensive and commonly measured in routine laboratory examination panels, could facilitate the prediction of non-obese individuals susceptible to T2DM.

Abbreviations

BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; T2DM, type 2 diabetes mellitus; WBC, white blood cell.

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Disclosure

The authors report no conflicts of interest in this work.

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