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The Association Between Hematological Indices and Type 2 Diabetes Mellitus in Iranian Population

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Abstract

Background: Hematological alterations have been observed in diabetes, with some studies showing controversial associations between specific hematologic parameters and type 2 diabetes mellitus (T2DM).

Objectives: This study aims to determine the association between hematological indices, specifically white blood cell (WBC) count, red cell distribution width (RDW), and platelet distribution width (PDW), and the presence of T2DM in an Iranian population, using data from the Bandare-Kong non-communicable diseases (BKNCD) cohort.

Methods: Data from the BKNCD cohort, which includes 4063 individuals aged 35 - 70 years, was used in this study. After excluding participants with conditions that could interfere with the analysis, 2318 subjects remained for final evaluation.

Results: Among the 2318 individuals, T2DM was present in 530 (22.9%). Binary logistic regression analysis revealed that the odds of T2DM increased by approximately 7% for every 109/L increase in WBC count, after adjusting for variables such as occupation, age, body mass index, sex, place of residence, education, smoking, marital status, systolic and diastolic blood pressure (DBP), and physical activity (adjusted odds ratio (aOR) = 1.066, 95% confidence interval (CI) = 1.003; 1.133, P = 0.039). Additionally, elevated PDW was associated with a 63% increase in the odds of T2DM (aOR = 1.625, 95% CI 1.159; 2.279, P = 0.005), while increased RDW was associated with decreased odds of T2DM (aOR = 0.801, 95% CI 0.716; 0.895, P < 0.001).

Conclusions: Elevated PDW and WBC counts in T2DM patients in this study suggest an inflammatory state and hypercoagulability. However, the paradoxically decreased RDW may be linked to poor glycemic control in these patients.

Keywords: Prospective Epidemiological Research in Iran (PERSIAN), Hematological Indices, Type 2 Diabetes Mellitus, Type 2 Diabetes Mellitus

1. Background

Diabetes mellitus is a chronic illness characterized by elevated blood glucose levels due to the body's inability to produce enough insulin or effectively use it (1). As the global prevalence of type 2 diabetes mellitus (T2DM) continues to rise, it presents significant challenges to healthcare systems worldwide. By 2030, an estimated 7,079 cases of T2DM per 100,000 individuals are expected globally, with increases anticipated in all regions (2).

T2DM is a leading cause of cardiovascular disease (CVD) and is associated with dyslipidemia, oxidative stress, thrombophilia, endothelial dysfunction, inflammation, hemostatic disorders, and atherogenic lipoprotein production (3). Hematological changes, including abnormalities in red blood cells (RBCs), white blood cells (WBCs), platelets, and the coagulation

system, are observed in T2DM patients, affecting their structure, function, and metabolism (4).

These hematological abnormalities in diabetes may result from increased reactive oxygen species (ROS) production and advanced glycation end products (AGEs) due to chronic hyperglycemia, leading to tissue damage, oxidative stress, and dysfunction in the vascular and hematological systems (5, 6). In T2DM patients, these alterations can exacerbate or contribute to conditions such as anemia, hypercoagulability, and CVD (7). Moreover, insulin resistance accelerates vascular complications through endothelial dysfunction, inflammation, and platelet hyperactivity (6).

2. Objectives

This study aims to explore the correlations between T2DM and hematological indices in the Iranian coastal city of Bandare-Kong.

3. Methods

3.1. Participants and Study Design

This study utilized data from the Bandare-Kong non-communicable diseases (BKNCD) cohort, which is part of the larger Prospective Epidemiological Research Studies in Iran (PERSIAN) initiative. Bandare-Kong non-communicable diseases collected data from 4063 individuals aged 35 - 70 years in Bandare-Kong, Hormozgan province, southern Iran, between November 2016 and November 2018. The cohort's methodology has been thoroughly described elsewhere (8). After excluding individuals with conditions that could interfere with the study, 2318 participants remained for analysis, including 530 with diabetes. Exclusion criteria included pregnancy, thyroid disorders, autoimmune diseases, inflammatory bowel disease, malignancies, liver diseases, chronic obstructive pulmonary disease, thalassemia, and hormonal disorders. Those undergoing chemotherapy or taking statins, coagulants, oral contraceptives, supplements, or alcohol were also excluded.

3.2. Data Collection, Variable Definition, and Laboratory Methods

Sociodemographic information, including age, occupation, sex, marital status, education, place of residence, and smoking status, was collected through in-person interviews. Body weight was measured using a mechanical scale with a 0.5 kg accuracy, while subjects wore minimal clothing and no shoes. Heights were measured with bare feet, standing with shoulders relaxed, using a stretch-resistant tape accurate to 0.5 cm. Body mass index was calculated to the nearest 0.01 by dividing weight (in kilograms) by the square of height (in meters).

After five minutes of rest, a trained nurse measured blood pressure (BP) with the subjects seated, feet flat, and arms at heart level. A standard mercury sphygmomanometer was used, with the cuff size adjusted for arm circumference. The average of two BP readings, taken five minutes apart, was recorded. If the systolic BP (SBP) differed by more than 10 mmHg or diastolic BP (DBP) by more than 5 mmHg, a third measurement was taken, and the closest two values were averaged.

Following a 10 to 12-hours fast, blood samples were collected and centrifuged at 1000 g for 10 minutes. Serum was separated and stored at -80°C until analysis. A chemistry autoanalyzer (BT1500) was used to measure total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) using a colorimetric method and standard kits (Pars Azmoon, Tehran, Iran) (Biotechnical Instruments, Rome, Italy). The Friedewald equation (LDL-C = TC - HDL-C - TG/5) was used to calculate low-density lipoprotein cholesterol (LDL-C), and for individuals with TG levels above 300 mg/dL, LDL-C was directly measured using a kit (Pars Azmoon, Tehran, Iran).

Whole blood samples were analyzed for complete blood count (CBC) using a Mindray BC 3000 automatic hematology analyzer (Mindray Corporation, China). Parameters measured included WBC count, hemoglobin (Hb), RBC count, hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, red cell distribution width (RDW), mean platelet volume (MPV), platelet crit (PCT), platelet distribution width (PDW), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR).

Diabetes was defined by the American Diabetes Association (ADA) as having an FPG of 126 mg/dL or higher, confirmed by a second test, and/or the use of glucose-lowering medication. Additionally, individuals who self-reported having diabetes were classified as diabetics.

Physical activity was defined as a combination of work, exercise, and leisure activities, measured as weekly metabolic equivalents of tasks (METs). Smoking status was self-reported, with current smokers defined as those having smoked at least 100 cigarettes in their lifetime, and ex-smokers defined as those who had smoked at least 100 cigarettes but had quit for at least six months.

3.3. Ethical Considerations

All participants provided written informed consent after being fully informed of the study's purpose. The study protocol was approved by the Hormozgan University of Medical Sciences Ethics Committee in accordance with the principles of the Helsinki Declaration (ethics code: IR.HUMS.REC.1398.473).

3.4. Data Analysis

Data were analyzed using SPSS version 25.0. Categorical variables were compared between diabetic and non-diabetic individuals using the chi-squared test, while continuous variables were compared using the independent *t*-test. Multivariable binary logistic regression was conducted to assess the relationship between hematological indices and T2DM, adjusting for relevant covariates. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported, with a P-value of less than 0.05 considered statistically significant.

4. Results

Overall, 2318 participants from the BKNCD cohort were evaluated in this study. The general characteristics of individuals with and without T2DM are compared in Table 1. Participants with T2DM were significantly older (mean age 53.77 vs. 46.38 years, $P < 0.001$), had a higher BMI (mean 27.73 vs. 26.24 kg/m^2, $P < 0.001$), and exhibited higher systolic (125.72 vs. 115.87 mmHg, $P < 0.001$) and diastolic blood pressure (DBP) (79.80 vs. 75.77 mmHg, $P < 0.001$) compared to those without T2DM. The T2DM group also had higher mean total cholesterol (204.34 vs. 199.19 mg/dL, $P = 0.036$) and triglyceride levels (167.89 vs. 125.77 mg/dL, $P < 0.001$), as well as lower physical activity levels (mean weekly metabolic equivalent of task (MET) 271.08 vs. 285.59, $P < 0.001$).

Regarding hematological indices, the T2DM group had significantly higher WBC counts (mean 7.60 vs. 6.85 $\times 10^9$/L, $P < 0.001$), higher PDW (mean 15.50 vs. 14.40%, $P < 0.001$), and lower RDW (mean 13.10 vs. 13.30%, $P = 0.043$) compared to non-diabetic individuals (Table 2).

Binary logistic regression analysis (Table 3) showed that after adjusting for age, sex, education, marital status, place of residence, occupation, smoking, BMI, SBP, DBP, and physical activity, each 10^9/L increase in WBC count was associated with a 7% higher odds of T2DM (aOR = 1.066, 95% CI 1.003; 1.133, $P = 0.039$). Additionally, each one percent increase in RDW decreased the odds of T2DM by approximately 20% (aOR = 0.801, 95% CI 0.716; 0.895, $P < 0.001$). Moreover, each one percent increase in PDW increased the odds of T2DM by 63% (aOR = 1.625, 95% CI 1.159; 2.279, $P = 0.005$).

5. Discussion

This population-based study revealed that, after controlling for potential confounders, WBC count, RDW, and PDW were significantly associated with T2DM. The association with WBC count and PDW was positive, while the correlation with RDW was negative.

We found that for every 10^9/L increase in WBC count, the odds of T2DM increased by approximately 7%. The mean WBC count was significantly higher in T2DM patients than in individuals without T2DM. Similar findings were reported by Ebrahim et al., although their results did not reach statistical significance, likely due to a smaller sample size and lack of adjusted analysis (9). Conversely, Twig et al. concluded that even within the normal range, WBC count was an independent risk factor for diabetes in young men (10). A systematic review and meta-analysis of 20 studies also indicated a higher risk of T2DM with elevated WBC, although the authors noted that the relationship may have been overestimated due to publication bias and incomplete adjustment for confounders (11). Other studies have also shown that WBC count independently predicts incident T2DM (12), though some, such as Mahdiani et al., found

Table 1. Comparison of General Characteristics Between Individuals with and Without Type 2 Diabetes Mellitus [a, b, c]

Variables	Diabetes (n = 530)	No Diabetes (n = 1788)	P-Value [b]
Socio-demographics			
Age (y)	53.77 (8.60)	46.38 (8.97)	< 0.001
Sex			
Male	226 (42.6)	898 (50.2)	0.002 [c]
Female	304 (57.4)	890 (49.8)	
Marital status			
Single	54 (10.2)	133 (7.4)	0.041 [c]
Married	476 (89.8)	1655 (92.6)	
Residence			
Urban	432 (81.5)	1594 (89.1)	< 0.001 [c]
Rural	98 (18.5)	194 (10.9)	
Occupation			
Unemployed	337 (63.6)	870 (48.7)	< 0.001 [c]
Employed	193 (36.4)	918 (51.3)	
Education (y)	4.14 (4.35)	6.46 (4.74)	< 0.001
Smoking	177 (33.4)	527 (29.5)	0.085 [c]
Anthropometrics			
BMI (kg/m^2)	27.73 (4.88)	26.24 (4.92)	< 0.001
Blood pressure			
SBP (mmHg)	125.72 (18.28)	115.87 (15.79)	< 0.001
DBP (mmHg)	79.80 (17.74)	75.77 (10.04)	< 0.001
Lipid profile (mg/dL)			
Total cholesterol	204.34 (52.31)	199.19 (39.00)	0.036
TG	167.89 (143.39)	125.77 (69.72)	< 0.001
LDL	124.58 (38.43)	126.98 (32.68)	0.770
HDL	47.23 (10.77)	47.38 (10.39)	0.192
Physical activity			
Weekly activity	271.08 (39.20)	285.59 (46.24)	< 0.001

Abbreviations: BMI, Body Mass Index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; METs, metabolic equivalent of tasks, number; SBP, systolic blood pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus; TG, triglyceride.

[a] Values are presented as No. (%) or mean (SD).

[b] Analyzed by independent *t*-test.

[c] Analyzed by chi-squared test.

no association between elevated WBC count and insulin resistance (13). Despite some inconsistencies, many studies link elevated WBC count with glucose metabolism disorders and diabetes complications (14, 15).

The link between chronic inflammation and T2DM has been widely studied, with low-grade inflammation thought to contribute to insulin resistance and metabolic dysfunction (16). Elevated WBC count, a classic marker of inflammation, may reflect the pro-inflammatory state in T2DM patients due to metabolic stress and oxidative damage in insulin-sensitive tissues (17, 18). This could explain our study's positive correlation between WBC count and T2DM, though the magnitude of this effect was relatively small.

Our study also found that each one percent increase in RDW decreased the odds of T2DM by nearly 20%. RDW, which measures variability in RBC size, is typically elevated in conditions associated with impaired erythropoiesis and systemic inflammation (19, 20). Increased RDW has been linked to poor prognosis in various conditions, including T2DM, as systemic inflammation and deficiencies in iron and folate may interfere with RBC production (21, 22). Interestingly, our study found that T2DM patients had significantly lower RDW levels compared to non-diabetic individuals, which contrasts with other studies reporting elevated RDW in T2DM patients (23-25). These differences may be related to glycemic control, as suggested by Alamri et al., who found that lower RDW values were associated with worse glycemic control (26). Although we could not assess glycemic control in our cohort, the lower RDW levels observed may indicate that many of our T2DM patients had uncontrolled diabetes.

Table 2 . Comparison of Hematological Indices Between Individuals with and Without Type 2 Diabetes Mellitus [a, b]

Variables	Diabetes (n = 530)	No Diabetes (n = 1788)	P-Value [b]
WBC count	6.82 (1.86)	6.42 (1.89)	< 0.001
RBC count	4.93 (0.66)	4.86 (0.65)	0.024
Hb (g/dL)	13.02 (1.94)	12.93 (1.99)	0.360
HCT (%)	39.47 (5.48)	39.02 (5.38)	0.096
MCV (fL)	80.47 (8.26)	80.94 (9.10)	0.262
MCH (pg)	26.52 (3.27)	26.75 (3.56)	0.170
MCHC (g/dL)	32.93 (1.74)	33.07 (1.95)	0.129
RDW (%)	14.17 (1.45)	14.34 (1.72)	0.043
Plt count ($\times 10^9$/L)	258.50 (83.94)	261.84 (74.30)	0.379
MPV (fL)	9.19 (0.80)	9.04 (0.82)	< 0.001
PDW (%)	15.50 (0.50)	15.42 (0.40)	< 0.001
PCT (%)	0.24 (0.07)	0.23 (0.06)	0.705
PLR	112.44 (42.91)	122.66 (43.65)	< 0.001
NLR	1.68 (0.62)	1.71 (0.72)	0.300

Abbreviations: Hb, hemoglobin; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; N, number; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PCT, plateletcrit; PLR, platelet-to-lymphocyte ratio; Plt, platelet; RBC, red blood cell; RDW, red cell distribution width; SD, standard deviation; T2DM, type 2 diabetes mellitus; WBC, white blood cell.

[a] All values are described as mean (SD).

[b] Analyzed by independent *t*-test.

Table 3. Binary Logistic Regression Analysis for the Association of Hematological Indices with Type 2Diabetes Mellitus

Independent Variables	cOR (95% CI)	P-Value	aOR (95% CI)	P-Value
Age (y)	1.088 (1.076; 1.100)	< 0.001	1.076 (1.061; 1.092)	< 0.001
Sex				
Male	1.000			
Female	1.357 (1.116; 1.650)	0.002	1.566 (1.072; 2.287)	0.020
Education (y)	0.888 (0.867; 0.910)	< 0.001	0.978 (0.949; 1.008)	0.144
Marital status				
Single	1.412 (1.013; 1.968)	0.042	0.836 (0.561; 1.246)	0.380
Married	1.000			
Residence				
Rural	1.000			
Urban	0.537 (0.412; 0.699)	< 0.001	0.519 (0.380; 0.708)	< 0.001
Occupation				
Unemployed	1.000			
Employed	0.543 (0.444; 0.663)	< 0.001	1.123 (0.813; 1.551)	0.481
Smoking	1.200 (0.975; 1.476)	0.085	1.167 (0.900; 1.514)	0.245
BMI (kg/m^2)	1.061 (1.041; 1.082)	< 0.001	1.073 (1.048; 1.099)	< 0.001
SBP (mmHg)	1.034 (1.028; 1.040)	< 0.001	1.022 (1.011; 1.033)	< 0.001
DBP (mmHg)	1.039 (1.029; 1.049)	< 0.001	0.985 (0.968; 1.003)	0.095
Weekly activity (METs)	0.991 (0.988; 0.993)	< 0.001	0.995 (0.992; 0.998)	0.002
WBC count ($\times 10^9$/L)	1.110 (1.057; 1.167)	< 0.001	1.066 (1.003; 1.133)	0.039
RBC count ($\times 10^{12}$/L)	1.186 (1.023; 1.375)	0.024	0.586 (0.173; 1.866)	0.352
HCT (%)	1.015 (0.997; 1.034)	0.097	1.096 (0.945; 1.272)	0.227
MCH (pg)	0.982 (0.955; 1.009)	0.190	0.814 (0.649; 1.021)	0.074
MCHC (g/dL)	0.963 (0.915; 1.014)	0.154	1.131 (0.939; 1.362)	0.195
RDW (%)	0.937 (0.879; 0.998)	0.043	0.801 (0.716; 0.895)	< 0.001
MPV (fL)	1.251 (1.112; 1.406)	< 0.001	1.071 (0.923; 1.244)	0.364
PDW (%)	1.713 (1.293; 2.270)	< 0.001	1.625 (1.159; 2.279)	0.005
PLR	0.994 (0.992; 0.997)	< 0.001	0.997 (0.994; 1.000)	0.096

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; T2DM, Type 2 diabetes mellitus.

Additionally, we found that PDW values were significantly higher in T2DM patients, and each one percent increase in PDW was associated with a 63% higher odds of T2DM. This finding aligns with studies by Atak et al. and others, which reported higher PDW values in T2DM patients, particularly those with poor glycemic control (27, 28). Platelet distribution width reflects variability in platelet size and is considered a marker of platelet activation (29, 30). T2DM patients are prone to increased platelet reactivity due to metabolic abnormalities, oxidative stress, and insulin resistance, which heighten their risk for hypercoagulability and cardiovascular complications (31, 32).

5.1. Strengths and Limitations

A key strength of this study is its population-based design and large sample size. Additionally, we controlled for many potential confounders in assessing the association between hematological indices and T2DM. However, there are several limitations. First, although BKNCD is a cohort study, we analyzed cross-sectional data from the first phase, preventing us from establishing causality. Second, logistic regression analysis tends to overestimate ORs, so the results should be interpreted cautiously. Third, we did not have data on the glycemic control status of T2DM patients, which may have influenced the results. Lastly, there was an age mismatch between the diabetes and non-diabetes groups, which could affect hematological indices despite age adjustment in the regression models.

5.2. Conclusions

Type 2 diabetes mellitus patients in this study exhibited increased WBC count and PDW, reflecting inflammation and hypercoagulability, while their RDW was surprisingly lower, potentially due to poor glycemic control. Future longitudinal data from the BKNCD cohort will help clarify the relationship between hematological indices and the development of T2DM over time.

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Footnotes

Authors' Contribution: M. K. designed and wrote the manuscript; M. S. supervised the study; S. R. performed the statistical analysis; S. M. H. and Y. M. wrote the manuscript; L. H., E. E., and M. S. A. were consulted on the possible factors to consider; V. J. revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interests Statement: The authors declare that they have no competing interests.

Data Availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval: The study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences under the ethics code IR.HUMS.REC.1398.473 ; and agrees with the statements of the Declaration of Helsinki.

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Informed Consent: Written informed consent was obtained from all the participants.

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