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ORIGINAL RESEARCH

Association of Hematological Parameters and Diabetic Neuropathy: A Retrospective Study

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Background: Diabetic neuropathy (DN) is a common complication of type 2 diabetes (T2DM) and is characterized by persistent inflammation. Hematological parameters have emerged as a novel marker for detecting chronic inflammatory conditions, including diabetes.

Aim: We aim to examine the association between HbA1c levels, which can indicate the presence of diabetic neuropathy, and hematological parameters to explore the possibility of using hematological parameters as a new indicator for DN in T2DM patients.

Methods: This was a retrospective study of 768 (483 males and 284 females) medical records of adult T2DM patients with or without neuropathy who attending the outpatient neuromuscular clinic at King Abdul-Aziz University Hospital from January 2016 to December 2021.

Results: The results showed significant increases in HbA1c levels (p=0.000), lymphocyte levels (p=0.028), and the neutrophil-lymphocyte ratio (NLR) (p=0.011). In the T2DM group, HBA1C levels were found to be positively correlated with age (r=0.306, p=0.000), neutrophil (NEUT) (r=0. 287, p=0.000), platelet (PLT) (r=0. 148, p=0.039), and neutrophil-lymphocyte ratio (NLR) (r=0.306193, p=0.0007), and negatively correlated with gender (r=−0.306193, p=0.0007). In the T2DMN group, HBA1C levels showed a positive correlation with hemoglobin (HB) (r=0.084, p=0.045), PLT (r=0.087, p=0.037), and PLT/mean corpuscular hemoglobin (MCH) ratio (PLT/MCH ratio) (r=0.12, p=0.004), and a negative correlation with age (r=−0.204, p=0.000), gender (r=−0.086, p=0.041), weight (WT) (r=−0.113, p=0.007), Body Surface Area (BSA) (r=−0.09, p=0.031), mean corpuscular volume (MCV) (r=−0.292, p=0.000), and MCH (r=−0.186, p=0.000).

Conclusion: Our study found a significant association between HbA1c, a biomarker for diabetic neuropathy, and various hematological parameters (HB, MCV, MCH, PLT, PLT/MCH ratio) in T2DMN patients. By effectively controlling and monitoring these variables, it may be feasible to prevent or delay the progression of peripheral neuropathy in diabetic patients. However, further research is needed to validate these findings.

Plain Language Summary: DN is nerve damage induced by elevated blood glucose levels in T2DM. It is a common condition that affects patients by increasing the chance of falling, causing discomfort, and decreasing their quality of life. It is one of the most ubiquitous consequences of diabetes. Symptoms include limb numbness, tingling, weakness, and severe pain and sensitivity. Long-term microvascular effects of diabetes mellitus include retinopathy, nephropathy, and neuropathy. This study was done to evaluate the effects of DN on hematological parameters. The haematological parameters study aims to identify a relationship between HbA1c and DN. The researchers determined clinical data through clinical records including age, gender, WT, BSA, and laboratory data included HbA1c, HB, MCHC, MCV, MCH, PLT, RDW, HCT, NEUT, LYMPH, NLR, PLR, and PLT/MCH ratio. Statistical analysis was applied after data collection. As a result, this retrospective study identified both positive and negative correlations between HbA1c, a biomarker for diabetic neuropathy, and haematological variables in diabetic patients with neuropathy, including HB, MCV, MCH, PLT, and the PLT/MCH ratio. This finding may be used as a prognostic indicator of DN. It is crucial to manage and monitor blood

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sugar levels for effective treatment of this dangerous condition. Doctors advise regular walking and mild exercise to reduce neuropathy discomfort, build muscle, and regulate blood sugar levels. An in-depth investigation is required to validate the function of these parameters.

Keywords: diabetic neuropathy, HbA1C, hematological profile, peripheral neuropathy, microvascular complications

Introduction

DN has been a significant concern and a complication of diabetes mellitus (DM). The number of people with DM has doubled during the past 20 years.[1] By 2045, it is projected that 628 million individuals worldwide will be affected by this disease, while the currently estimated cases of DN stand at approximately 425 million.[1] According to statistics, 179 million people can have DM but remain undiagnosed for various reasons.[1] Due to ageing demographics, low levels of physical exercise, and urbanization, the number of people with T2DM has been expanding.[2] DN is a widespread ailment that tremendously impacts patients by elevating the risks of falls, causing discomfort, and decreasing the quality of life. DN is a nerve injury that starts in the longest nerves, which are supplied throughout the foot and then advance anteriorly. High levels of blood glucose damage the peripheral nerves resulting in disabilities. Symptoms noted in patients with DN are Numbness in limbs, tingling sensation, weakness in the body, and experiencing sharp pain and sensitivity.[3] Retinopathy, nephropathy, and neuropathy are long-term microvascular consequences of DM. DN typically begins affecting the legs and feet first and gradually progresses to the arms and hand region. According to the American Diabetes Association, approximately 50% of the population living with DM is affected by DN; therefore, the primary intervention of screening individuals to prevent DM is crucial.[4] However, regarding the scientific knowledge that hemoglobin is associated with kidney diseases and adverse diabetic effects, a high probability of renal dysfunction is predicted in DN due to damage to the nerves in the kidney region. Hemoglobin levels are high, around 18.8 g/dl in people with type 1 diabetes (T1DM) and overt nephropathy, compared with the general population suffering from renal disease.

Hematological parameters such as white blood count (WBC), Mean Platelet volume (MPV), plateletcrit (PCT), PLT, NLR, lymphocyte to monocyte ratio (LMR), and others are indicators of endothelial dysfunction and inflammation due to the result of their continued renewal over a lengthy duration of time. Evaluation of inflammatory parameters and potential risk markers can be done using these conventional and straightforward measures. The hematological parameters study aims to find the association between HbA1c and hematology markers and determine whether there is a significant correlation between the microvascular complications of DM and these parameters.[5] Numerous studies have linked an increased prevalence of neuropathy to the length of DM and HbA1c levels. HbA1c is a form of hemoglobin molecule to which a sugar molecule is chemically attached. The HbA1c test estimates the average blood sugar levels present in the body. When the percentage of glucose in the blood increases, the glucose bond with hemoglobin molecules in a concentration-dependent manner. This mechanism increases the HbA1c levels in the bloodstream, which are then detected in the estimation for DM. Its concentration depends upon the plasma glucose concentration and the length of hyperglycemia. It measures how substantially DM control has progressed over twelve weeks.[5] The HbA1c levels are directly proportional to blood glucose levels.[1] It is the most common test for determining and controlling the blood sugars causing DM. DN often affects the legs and feet. According to Hicks et al[5] the mean Red Blood Cell count of a diabetic patient with HbA1c<7 is less than a person who does not have DM. A decrease was noted in mean hemoglobin, red blood cell (RBC), hematocrit, and MCV of diabetic patients with HbA1c>7 as compared to those without DM with HbA1c> as compared to hbA1c<7.[5]

Low calcium levels and high uric acid in diabetic peripheral neuropathy (DPN) are evident in diabetic patients as calcium is a critical mineral that regulates a broad range of physiological and biological functions, including muscular contraction, nerve impulse transmission, insulin secretion, and glucose homeostasis. The neutrophil-to-lymphocyte ratio has been proposed as the biomarker of systemic inflammation, a leading cause of morbidity following a cardiac event, and an indicator of cancer outcomes. Identification of diabetic inflammation and its complications, including neuropathy and macro-vascular disease, is done by determining the neutrophil-to-lymphocyte ratio.[6] According to (Cardoso et al, 2021a), NLR is the mainstream method to investigate microvascular complications caused by DN as it connects two

distinct pathways that trigger the inflammatory response.[7] Neutrophils are closely associated with the inflammation process, while lymphocytes influence the progression of the immune response. Compared to non- DPN, the NLR is consistently significantly higher in patients suffering from DPN due to hoisted HbA1c levels and poor glycemic control. Hyperglycemia suppresses neutrophil activity by elevating intracellular calcium concentrations and lowering adenosine triphosphate (ATP) levels.[8] Low counts of lymphocytes and leukocyte ratios are predictors of mortality and macrovascular impediments in people with T2DM. In cardiovascular mortality, the ratio of neutrophil to lymphocyte and lymphocyte to platelet ratio is attributed to the increased risks for mortality. Higher lymphocyte counts were beneficial, while higher monocyte counts were detrimental. Several lymphocyte-containing leukocyte ratios predicted cardiovascular fatalities.[7]

These hematological parameters shift in paradigm plays an essential and crucial role in microvascular and microvascular complications of DM.[9] It is, therefore, an utmost important task to evaluate and investigate each hematological parameter, including WBC, RBC, HB, MCH, MCHC, hematocrit, RBC distribution width, and MPV. In this retrospective study, we further discuss the association between glycated hemoglobin and other hematological parameters to assess the onset of DN.[9]

Literature Review

According to WHO, an average Non-diabetic HbA1c level ranges from 4.0% to 5.6%. Its values in prediabetes range from 5.7% to 6.4%, while those with HbA1c levels of 6.4% or more significant have DM.[1] The nerve vessels in the foot region get damaged due to high blood glucose levels, causing the tissue to die and resulting in the skin's purple, red or black color. The microvascular complication is associated with long-term hyperglycemia depending on time or period.[1] According to reports, DPN is correlated to factors like glycemic exposure, the length of time a person has had DM, insulin resistance, visceral adiposity, dyslipidemia, and hypertension.[10] Therefore, one risk variable related to microvascular issues is the degree to which HbA1c levels might fluctuate. To represent the correlation between DPN and CV-HbA1c in T2DM patients and to assess the effects of M-HbA1c and CV-HbA1c in all DPN patients at risk, the study was carried out in China following the recommendations of the American Diabetes Association. They found that the percentage of HbA1c patients who suffered from DPN considerably increased from 6.9% in the first tertile to 1.19% in the second tertile to 28.5% in the third tertile. This was a considerable increase from the beginning of the study.[10]

A study was conducted at the University of Gondar in northwest Ethiopia, which aimed to estimate FBS levels and blood indices such as size and content of red blood cells using Sysmex-XK 21N analyzers and Bio Systems A25. The findings revealed a significant disparity in the red blood cell distribution between DM patients and the control group.[2] The study found that individuals with an HbA1c level above 7 had a decreased average red blood cell count compared to non-diabetic adults. Patients with T2DM who have HbA1c levels above 7 tend to exhibit lower red blood cell count, hemoglobin levels, and hematocrit levels compared to individuals without diabetes. The study revealed that there was a decrease in the median values of MCV and MCH in diabetic individuals with HbA1c levels above 7 compared to those with HbA1c levels below 7. Additionally, when compared to non-diabetic individuals, diabetic patients had lower mean levels of HB, PCV, RBC, MCH, and MCV.[5]

According to a study at King Abdul Aziz University, excessive protein in the urine indicated significant DN. The baseline level of HbA1c was intimately correlated to loss of sensation, the feeling of touch, and temperature detection. According to this interpretation of epidemiologic data, glycemic management is linked to the emergence and growth of diabetic microvascular disorders in Non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM).[11]

According to research conducted in India,[12] increased HbA1c levels over time have been associated with alterations in hemoglobin's structure and function, cytoplasmic drag brought on by viscosity, and osmotic imbalances in Red blood cells. The results also revealed that patients with HbA1c levels above seven have significantly lower mean MCV and MCH values than DM patients with HbA1c levels below seven.[5]

Research at Baqai University in Pakistan found significant differences in fasting blood glucose, HbA1c, MPV, PDW, and hs-CRP levels in diabetic patients, potentially identifying complications in DN.[13] Furthermore, contradicting evidence suggests no connection and dependence between platelet and DN.[14]

The 2004–2009 Rio de Janeiro research comprised 689 people with T2DM. The neutrophil-to-lymphocyte ratio, monocyte-to-high-density lipoprotein ratio, and monocyte count ratio were all linked to cardiovascular deaths, whereas

the lymphocyte-to-monocyte ratio was safe and protective. Higher lymphocyte-to-monocyte ratios help insulin-dependent diabetics avoid renal impairments and failures. Lymphocytes protect the kidneys. Low lymphocyte numbers and leukocyte fractions primarily comprised of lymphocytes indicate microvascular concerns. Unfortunately, compared to known adverse effects, they did not improve risk predictions.[7] According to an investigation of hematological parameters performed in Ethiopia, diabetic patients have significant disparities in their neutrophil, lymphocyte, basophil, eosinophil, and white blood cell count.[15]

T2DM patients have inflammatory pathophysiology. In a cohort study conducted in China, Researchers discovered that a greater RDW concentration was linked to an increased probability of developing T2DM which can subsequently lead to DPN. It was also studied that DPN has been associated with various inflammatory biomarkers, including interleukin-1 (IL1, IL8, IL6, TNF, and TGF beta one), together with cytokines.[16]

According to the findings of previous investigations in Turkey and Bangladesh, based on the WBC indexes determined in the research, the T2DM experimental group had a considerably higher total WBC count.[17] A Saudi Arabian analysis revealed that the absolute eosinophil and basophil counts were substantially higher in the DM group than in the control research group.[17]

An investigation on anthropometric and hematological markers of T2DM was performed in northeastern Ethiopia. They identified a relationship between the MPV, the platelet, and the RDW and RBC concentration. The prevalence of DM is related to the study's findings. Examining hematological changes in insulin-dependent diabetic patients will make them critically unhealthy. To prevent critical conditions, Experts will devise an efficient and therapeutic treatment. Physicians prefer the largest sample size possible in a research study, 15 for a complete condition analysis.

The experiment's primary observation was that, compared to subjects with normal albumin levels, NLR levels correlated with the individuals diagnosed with early-stage DPN. The post-prandial blood sugar (PPBS), fasting blood sugar (FBS), and HbA1c measures for hyperglycemia indicate no significant changes between the two groups, even though HbA1c has been demonstrated in a prior study to be a distinct risk factor for DN in other research.[7] This study examined the correlation between HbA1c (DN biomarker) and CBC parameters regarding the future risk for T2DMN.

The results and conclusions of prior studies are listed in Table 1 below.

Materials and Methods

Study Population

From January 2016 to December 2021, a retrospective study was done using data obtained from individuals diagnosed with T2DM and T2DMN. 768 patients over the age of 20 in total. Medical College, KAU's Biomedical Research Committee evaluated and approved the research protocol (Study Number 146–22). As this was retrospective research using clinical data extracted from medical records, informed permission was unnecessary.

The study's inclusion and exclusion criteria are as follows: Inclusion criteria consist of being at least 20 years old and meeting the diagnostic criteria for T2DM. Exclusion criteria include patients with type 1 diabetes, Guillain-Barré syndrome, severe cervical and lumbar neuropathy, rheumatoid arthritis or other medications that affect peripheral nerves, sequelae of cerebrovascular disease or lumbar vertebral disease, hereditary neuropathy, or a history of neurosurgery.

Clinical Variables

Clinical data were collected, including age, gender, WT, BSA, and laboratory data included HbA1c, HB, MCHC, MCH, PLT, RDW, HCT, NEUT, LYMPH, NLR, PLR and PLT/MCH ratio. NLR, PLR, and PLT/MCH ratios were calculated from CBC parameters as the ratio of neutrophils to lymphocytes, platelets to lymphocytes, and platelets to mean corpuscular hemoglobin, respectively. Body surface area (BSA), by using mathematical formulas, body size was calculated from both weight and height. A BSA is a fundamental anthropometric measurement for more accurate metabolic mass and body size estimates. The BSA was collected retrospectively from medical records in our study.

Table 1 Indicating the Results and Conclusions of Previous Studies

Author	Year	Title	Methods	Results and Conclusion	Reference
Cardoso et al	2021	Importance of hematological parameters for micro- and macrovascular outcomes in patients with type 2 diabetes.	Prospective study	Low lymphocytes count and leukocyte ratios that mainly included lymphocytes were predictors of macrovascular complications. The lymphocytes count and the lymphocyte-to-monocyte ratio was protective (hazard ratios [HRs]: 0.77 and 0.72, respectively), whereas the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were associated with increased risks (HRs: 1.19 and 1.17) for all-cause mortality. For cardiovascular mortality, the monocytes count, the neutrophil-to-lymphocyte, and monocyte-to-HDL ratios were associated with increased risks, and the lymphocyte-to-monocyte ratio was protective.	Cardoso CR, Leite NC, Salles GF. Importance of hematological parameters for micro-and macrovascular outcomes in patients with type 2 diabetes: the Rio de Janeiro type 2 diabetes cohort study. *Cardiovascular Diabetology.* 2021;20(1):1–13[7]
Duran & Uludağ	2020	Can platelet count, mean platelet volume and red cell distribution width be prognostic factors for mortality in the intensive care unit?	Hospital-based descriptive study	The study showed that the difference between PLT, MPV, and RDW values in the ICU and values before death and a decrease in PL T and increase in MPV and RDW in all patients were statistically significant. In ICU. Entry in all patient groups and laboratory markers before exit, the value of the input RDW was 14.66 ± 3.08, and the output RDW was 15.94 ± 9.59. The admission value of MPV was 8.180 ± 2.09, and before death, the value of MPV was 9.199 ± 2.24. Statistically, it was significantly high ($p < 0.001$). The MPV values increased in all groups, and cerebrovascular disease (CVD), respiratory failure, cardiac causes, head trauma, and malignancies were statistically significantly high ($p < 0.05$). The admission value of PLT was 215.46 ± 116.8; before death, the value of PLT was 154.73 ± 101.32. Statistically, it was significantly low ($p < 0.001$).	Can platelet count and mean platelet volume and red cell distribution width be used as a prognostic factor for mortality in intensive care unit?[18]
Adnan & Aasim	2020	Prevalence of type 2 diabetes mellitus in the adult population of Pakistan: a meta-analysis of prospective cross-sectional surveys.	Prospective cross-sectional study	Diabetic type 2 is correlated with HbA1c.	Adnan M, Aasim M. Prevalence of type 2 diabetes mellitus in adult population of Pakistan: a meta-analysis of prospective cross-sectional surveys. Annals of global health. 2020;86(1).[17]
Wang et al	2020	The relationship between red blood cell distribution width and incident diabetes in Chinese adults.	Cohort study	High RDW was associated with a high risk of developing Diabetes in Chinese adults. Each unit increase of RDW was associated with a 16% higher risk of incident diabetes.	Wang J, Zhang Y, Wan Y, Fan Z, Xu R. The relationship between red blood cell distribution width and incident diabetes in Chinese adults: a cohort study. Journal of diabetes research. 2020;202.[16]

(*Continued*)

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Table 1 (Continued).

Author	Year	Title	Methods	Results and Conclusion	Reference
Bhutto et al	2019	Correlation of hemoglobin A1c with red cell width distribution and other parameters of red blood cells in type II diabetes mellitus.	Cross-sectional analytic study	The mean hemoglobin of patients was 11.59±1.315 gm/dl. The mean corpuscular volume (MCV) was 76.65 ±11.121 fL, and the mean RDW was found to be 18.287 ±4.352, with the highest value of 30.20. The mean MCH was 30.223±23.873 pg, with the highest value of 38.4 pg. The mean cell hemoglobin concentration (MCHC) was 28.214±4.7498 mg/dl. The HbA1c of the study population was found to be moderately uncontrolled, and the mean HbA1c was 8.278±5.015%, with the highest value of 16.2%. The mean fasting blood sugar was 158±39.50 mg/dl, while the mean random blood sugar was 236±57.390 mg/dl. The correlation of HbA1c with RDW turned out to be significant statistically (p-0.035), while other RBCs and hematological parameters, such as MCV, hemoglobin, and platelets, revealed no significant correlation.	Bhutto AR, Abbasi A, Abro AH. Correlation of hemoglobin A1c with red cell width distribution and other parameters of red blood cells in type II diabetes mellitus. Cureus. 2019;11(8).[12]
Farooqui et al	2019	Role and Significance of hematological parameters in diabetes mellitus.	Descriptive analytic study	Diabetic patient with poor control is more prone to anemia. The mean RBC count of people with diabetes with HbA1c<7 was less when compared to non-diabetic individuals. A significant decrease was noted in the mean RBC count, Hb, H.C.T., and MCV of people with diabetes with HbA1c>7 compared to non-diabetic individuals. There was a significant decrease in mean Hb, HCT, MCV, and MCH of people with diabetes with HbA1c >7 compared to people with diabetes with HbA1c <7.	Farooqui R, Afsar N, Afroze IA. Role and significance of hematological parameters in diabetes mellitus. Annals of Pathology and Laboratory Medicine. 2019;6(3):158–162.[5]
Su et al	2018	HbA1c variability and DPN in T2DM patients.	Cross-sectional study design	Increased HbA1c is closed related to DPN	Su J-b, Zhao L-h, Zhang X-l et al HbA1c variability and DPN in T2DM patients. Cardiovascular diabetology. 2018;17(1):1–9.[10]

Biadgo et al	2016	Hematological indices and their correlation with fasting blood glucose level and anthropometric measurements in type 2 diabetes mellitus patients in Gondar.	Comparative cross-section design	Hematological indices could be a valuable indicator of microvascular complications and glycemic control. There was a significant difference in red blood cell distribution width (47.3±2.6 fL vs 45.2±3 fL) between diabetic patients and controls. Total white blood cells in 103/μL (6.59±1.42 vs 5.56±1.38), absolute lymphocyte count in 103/μL (2.60±0.70 vs 2.04±0.63), and absolute neutrophil count in 103/μL (3.57±1.46 vs 3.11±1.04) increased significantly in diabetic patients compared with controls, respectively. Among platelet indices, mean platelet volume (10.4±1.1 fL vs 9.9±1.1 fL) and platelet distribution width (14.5±2.1 fL vs 13.4±2.1 fL) were found to be significantly increased in the diabetic patients ($P<0.05$).	Biadgo B, Melku M, Abebe SM, Abebe M. Hematological indices and their correlation with fasting blood glucose level and anthropometric measurements in type 2 diabetes mellitus patients in Gondar, Northwest Ethiopia. Diabetes, metabolic syndrome and obesity: targets and therapy. 2016;9:91.[2]
Sherwan et al	2016	Significance of HA1c test in diagnosis and prognosis of diabetic patients.[1]	Prospective cross-sectional study	High HbA1c is associated with long-term uncontrolled diabetic	Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomarker insights. 2016;11: BMI. S38440.[1]
Bhatta et al	2012	Mean platelet volume and platelet count in patients with type 2 diabetes mellitus.	Hospital-based descriptive study	Mean platelet volume was significantly higher in the diabetic and impaired fasting glucose group (7.40 ± 0.77 fL and 6.62 ± 0.58 fL), respectively, as compared to the non-diabetic group (6.06 ± 0.41 fL) ($p<0.001$). There was no significant difference in the platelet count between the three groups ($p=0.869$). A significant correlation was seen between rising fasting blood sugar and mean platelet volume ($r=0.559$; $p<0.001$), while no correlation existed between platelet count and fasting blood sugar level ($r=0.037$; $p=0.526$). Mean platelet volume increases in patients with type 2 diabetes mellitus and impaired fasting glucose.	Bhatta S, Singh S, Gautam S, Osti BP. Mean platelet volume and platelet count in patients with type 2 diabetes mellitus and impaired fasting glucose. Journal of Nepal Health Research Council. 2018;16(41):392–395.[14]
Fawwad, Rizvi & Alvi	2012	Role of platelet indices, glycemic control, and hs-crp in the pathogenesis of vascular complications in type-2 diabetic patients.	Comparative descriptive study	Poor glycemic control is positively related to HbA1c level. The increased values of MPV, PDW, and elevated hs-CRP level may also serve as a confirmatory test in finding the risk of developing complications. The study demonstrated that F.B.G., HbA1c, M.P.V., PDW, and hs-CRP were statistically higher in people with diabetes than in control subjects (P is less than 0.05). Positive correlation of FBG with HbA1c (r is equal to 0.993, P is equal to 0.0001), PLT with PCT (r is equal to 0.922, P is equal to 0.0001), and MPV with PDW (r is equal to 0.332, P is equal to 0.024) was found in diabetics.	Al-Shehri FS. Glycemic Control and Microvascular Complications of Type 2 Diabetes among Saudis. Journal of diabetes mellitus. 2019;9(4):167–175.[11]

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Statistical Analysis

Descriptive statistics characterized variables. Continuous variables were presented as median followed by the interquartile range 25–75 (IQR) and categorical variables as a percentage (%) and number (n). The Kolmogorov–Smirnov test determined data distribution normality. A nonparametric Mann–Whitney U (MWU) test assessed group differences. Spearman correlation analyzed the HbA1c-CBC relationship. The Chi-square test assessed categorical variables. We assumed 0.05 significance. SPSS 28.0 analyzed data (Chicago, IL, USA).

Results

The study included a total of 768 patients with T2DM, and their demographics are presented in Tables 2 and 3. The patients were divided into two groups based on the presence of DN: T2DM without neuropathy (T2DM, n=196) and T2DM with neuropathy (T2DMN, n=572). Among the participants, there were 284 females and 483 males.

Comparison of Hematological Among Study and Gender Groups

The Chi-Square Test analysis revealed a clear difference in the gender distribution between the T2DM group and the T2DMN group. The MWU test was used for statistical analysis, which showed significant increases in HbA1c (p=0.000),

Table 2 Comparison of Clinical Profile and Hematological Parameters Among Main Study Groups

Groups	**T2DM (25.5%) (N=196)**	**T2DMN (74.5%) (N=572)**	**P value**
Variables	**Median (IQR)**	**Median (IQR)**	**MWUT**
Age (year)	58 (50–65)	59 (50–66)	0.379
Gender male/female	62/133	222/350	0.000
WT (Kg)	76.45 (67–88)	77 (65–91)	0.922
BSA (m2)	1.78 (1.67–1.92)	1.81 (1.65–1.95)	0.697
HBA1c (%)	6.545 (6.1–7.1)	8 (6.8–9.49)	0.000
HB (g/dl)	12.5 (11.4–13.67)	12.4 (11.3–13.57)	0.399
HCT (%)	38.35 (35.9–40.95)	37.9 (34.73–41.37)	0.221
MCV (fL)	84.25 (79.82–88.65)	83.8 (79.3–87.5)	0.279
MCH (pg)	27.5 (25.72–29.27)	27.6 (25.7–28.9)	0.624
MCHC (%)	32.6 (31.7–33.3)	32.7 (31.8–33.6)	0.295
RDW-CV	14 (13.13–15.28)	13.9 (13–15.1)	0.36
NEUT (k/UL)	2.68 (1.9–3.12)	2.5 (1.83–3.21)	0.289
LYMPH (k/UL)	3.57 (2.6–4.91)	4.03 (2.75–5.64)	0.028
PLT (K/uL)	282.5 (226–336.5)	279 (230–335.75)	0.891
NLR	1.35 (0.97–2.02)	1.58 (1.05–2.44)	0.011
PLR (%)	109.27 (85.51–147.83)	110.13 (82.9–157.21)	0.502
PLT/MCH ratio	10.25 (8.22–12.7)	10.12 (8.29–12.93)	0.825

Note: P-value < 0.05.

Abbreviations: T2DM, type 2 diabetes mellitus; T2DM, T2DM with neuropathy; MWU, Mann–Whitney *U*-test; IQR, interquartile range; HBA1c, glycated haemoglobin; WT, weight; BSA, body surface area; HB, hemoglobin; MCV, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; PLT, platelet; RDW, red blood cell distribution width; HCT, hematocrit; NEUT, neutrophil; LYMPH, lymphocytes; PLR, Platelet-Lymphocyte Ratio; PLT/MCH: ratio, platelet count/mean corpuscular hemoglobin ratio; NLR, neutrophil-lymphocyte ratio.

Table 3 Comparison of Clinical Profiles and Hematological Parameters Among Gender Groups

Groups	Male (37%) (N=284)	Female (63%) (N=483)	P value
Variables	**Median (IQR)**	**Median (IQR)**	**MWUT**
Age (year)	61 (51–68)	58 (50–65)	0.03
WT (Kg)	77.4 (67–92)	76.3 (65–89.7)	0.107
BSA (m2)	1.87 (1.73–2.02)	1.77 (1.62–1.89)	0.000
HBA1c (%)	7.8 (6.8–9.3)	7.3 (6.3–8.69)	0.000
HB (g/dl)	13.4 (12.1–14.7)	12.1 (11.2–13)	0.000
HCT (%)	40.6 (36.6–44.15)	37.2 (34.6–39.4)	0.000
MCV (fL)	83.8 (79.3–87.65)	83.9 (79.6–87.6)	0.976
MCH (pg)	27.8 (25.8–29.45)	27.4 (25.6–28.9)	0.023
MCHC (%)	32.9 (32.1–33.9)	32.5 (31.6–33.3)	0.000
RDW-CV	13.8 (13–15.25)	13.9 (13.1–15.1)	0.661
NEUT (k/UL)	2.32 (1.6–2.99)	2.68 (1.96–3.36)	0.000
LYMPH (k/UL)	4.01 (2.6–5.88)	3.83 (2.78–5.2)	0.374
PLT (K/uL)	256 (215–319)	293 (242–346)	0.000
NLR	1.72 (1.03–2.77)	1.45 (1.01–2.07)	0.001
PLR (%)	116.17 (86.29–162.94)	108.15 (82.84–149.41)	0.052
PLT/MCH ratio	9.2 (7.63–11.74)	10.66 (8.68–13.42)	0.000

Note: P-value < 0.05.

Abbreviations: MWUT, Mann–Whitney *U*-test; IQR, interquartile range; HBA1c, glycated haemoglobin; WT, weight; BSA, body surface area; HB, hemoglobin; MCV, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; PLT, platelet; RDW, red blood cell distribution width; HCT, hematocrit; NEUT, neutrophil; LYMPH, lymphocytes; PLR, Platelet-Lymphocyte Ratio; PLT/MCH ratio, platelet count/mean corpuscular hemoglobin ratio; NLR, neutrophil-lymphocyte ratio.

LYMPH (p=0.028), and NLR (p=0.011) levels in T2DMN group compared to the T2DM group, as shown in Table 2. When considering gender, Table 3 indicated significant variations in age (p=0.03), BSA (p=0.000), HbA1c (p=0.000), HB (p=0.000), HCT (p=0.000), MCH (p=0.023), MCHC (p=0.000), NEUT (p=0.000), PLT, NLR (p=0.001), and PLT/MCH ratio (p=0.000) among study groups.

Correlation of Hba1c with Hematological Parameters

We conducted a Spearman correlation analysis to examine the association between Hba1c and various parameters. Our findings demonstrated positive correlations between Hba1c and age (r=0.306, p=0.000), NEUT (r=0.287, p=0.000), PLT (r=0.148, p=0.039), and NLR (r=0.193, p=0.007) in individuals with T2DM. Additionally, we observed a negative correlation between Hba1c and gender (r= −0.193, p=0.007). Also, Hba1c levels showed a positive correlation with HB (r=0.084, p=0.045), PLT (r=0.087, p=0.037), and PLT/MCH ratio (r= 0.12, p=0.004), and a negative correlation with age (r= −0.204, p=0.000), gender (r= −0.086, p=0.041), WT (r= −0.113, p=0.007), BSA (r= −0.09, p=0.031), MCV (r= −0.292, p=0.000), MCH (r= −0.186, p=0.000) among T2DMN group, as illustrated in Table 4. In addition, we correlated Hba1c with gender (male and female) groups. We found that Hba1c was positively correlated to LYMPH (r= 0.117, p=0.049), PLT (r=0.122, p=0.04), and PLT/MCH ratio (r= 0.163, p=0.006), and negatively correlated to age (r= −0.152,

Table 4 Spearman Correlation Coefficients for the Association Between Hba1c and Hematological Variables Among Study Groups

Groups	T2DM (25.5%) (N=196)		T2DMN (74.5%) (N=572)	
Variables	**Correlation Coefficient**	**P values**	**Correlation Coefficient**	**P values**
Age	0.306	0.000	−0.204	0.000
Gender	−0.193	0.007	−0.086	0.041
WT	−0.013	0.856	−0.113	0.007
BSA	0.015	0.832	−0.09	0.031
HB (g/dl)	0.084	0.24	0.084	0.045
HCT (%)	0.078	0.277	0.065	0.119
MCV (fL)	−0.085	0.236	−0.292	0.000
MCH (pg)	−0.049	0.493	−0.186	0.000
MCHC (%)	0.069	0.34	0.051	0.222
RDW-CV	−0.064	0.371	−0.07	0.092
LYMPH (k/UL)	0.078	0.276	0.045	0.286
NEUT (k/UL)	0.287	0.000	0.05	0.228
PLT (K/uL)	0.148	0.039	0.087	0.037
NLR	0.193	0.007	0.01	0.814
PLR (%)	0.006	0.937	0.019	0.644
PLT/MCH ratio	0.137	0.056	0.12	0.004

Note: P-value < 0.05.

Abbreviations: T2DM, type 2 diabetes mellitus; T2DMN, T2DM with neuropathy; WT, weight; BSA, body surface area; HB, hemoglobin; MCV, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; PLT, platelet; RDW, red blood cell distribution width; HCT, hematocrit; NEUT, neutrophil; LYMPH, lymphocytes; PLR, Platelet-Lymphocyte Ratio; PLT/MCH ratio, platelet count/mean corpuscular hemoglobin ratio; NLR, neutrophil-lymphocyte ratio.

p=0.01), gender (r= −0.127, p=0.033), BSA (r= −0.127, p=0.033), MCV (r= −0.329, p=0.000), MCH (r= −0.183, p=0.002), RDW-CV (r= −0.149, p=0.012) among the male group. Also, we found that Hba1c had a positive correlation to NEUT (r= 0.161, p=0.000), PLT (r=0.118, p=0.01), NLR (r=0.119, p=0.009), and PLT/MCH ratio (r= 0.142, p=0.002), and a negative correlation to MCV (r= −0.197, p=0.000), MCH (r= −0.155, p=0.001) among the female group, as presented in Table 5.

Discussion

The high prevalence of DM and its complications, including DPN, present a significant public health concern. DPN often results in neuropathic pain, foot ulcers, and the necessity for lower limb amputation, greatly affecting the quality of life of those affected.[19] Previous studies have emphasized the link between DPN and HbA1c in individuals with T2DM. Multiple studies have been conducted to examine this relationship, providing valuable insights. Su et al conducted a study that found a strong connection between increased HbA1c variability and DPN, suggesting that HbA1c variability can be a reliable indicator for DPN.[10] Another study by Lai et al discovered that both HbA1c variability and chronic glycemic impairment were significantly associated with the severity of peripheral neuropathy in type 2 diabetes

Table 5 Spearman Correlation Coefficients for the Association Between Hba1c and Hematological Variables Among Gender Groups

Groups	Male (37%) (N=284)		Female (63%) (N=483)	
Variables	**Correlation Coefficient**	**P values**	**Correlation Coefficient**	**P values**
Age	−0.152	0.01	−0.067	0.142
WT	−0.127	0.033	−0.066	0.145
BSA	−0.127	0.033	−0.074	0.107
HB (g/dl)	0.09	0.129	−0.034	0.452
HCT (%)	0.064	0.283	−0.052	0.252
MCV (fL)	−0.329	0.000	−0.197	0.000
MCH (pg)	−0.183	0.002	−0.155	0.001
MCHC (%)	0.065	0.277	0.036	0.432
RDW-CV	−0.149	0.012	−0.034	0.451
LYMPH (k/UL)	0.117	0.049	0.023	0.611
NEUT (k/UL)	0.031	0.603	0.161	0.000
PLT (K/uL)	0.122	0.04	0.118	0.01
NLR	−0.039	0.513	0.119	0.009
PLR (%)	−0.063	0.289	0.052	0.256
PLT/MCH ratio	0.163	0.006	0.142	0.002

Note: P-value < 0.05.

Abbreviations: WT, weight; BSA, body surface area; HB, hemoglobin; MCV, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; PLT, platelet; RDW, red blood cell distribution width; HCT, hematocrit; NEUT, neutrophil; LYMPH, lymphocytes; PLR, Platelet-Lymphocyte Ratio; PLT/MCH ratio, platelet count/mean corpuscular hemoglobin ratio; NLR, neutrophil-lymphocyte ratio.

patients.[20] This reinforces the importance of intensive blood glucose control within an acceptable range and personalized treatment to prevent further nerve damage. Casadei et al conducted a study that highlighted the use of high HbA1c levels as a strategic biomarker for detecting peripheral neuropathy in diabetic foot patients.[19] This study also supported the idea that intensive glycemic control and lower HbA1c levels effectively reduce the risk of diabetic complications, including peripheral neuropathy. Furthermore, a study conducted by Bansal et al demonstrated that each 1% increase in HbA1c corresponds to a 10–15% increased risk of developing diabetic neuropathy.[18] Additionally, Nathan et al provided evidence supporting that keeping HbA1c levels below 7 is linked to a 60% decrease in the occurrence of peripheral neuropathy.[21] Therefore, it is crucial to assess HbA1c levels in order to monitor blood sugar fluctuations and predict the risk of complications. By analyzing the findings of these studies, we can use HbA1c to establish connections with blood-related factors, as diabetes often affects hematological parameters, leading to alterations in function, shape, and metabolism.[22] This retrospective study aimed to assess the correlation between HbA1c levels and hematological parameters to evaluate the potential risk of DPN.

Our study found that T2DMN patients had higher levels of HbA1c, lymphocytes, and NLR compared to the T2DM group. There was a positive correlation between HbA1c levels and age, neutrophil count, platelet count, and NLR. On the other hand, there was a negative correlation between HbA1c levels and gender in the T2DM group. In the T2DMN group, HbA1c levels were positively correlated with HB levels, PLT, and PLT/MCH ratio, while negatively correlated

with age, gender, MCV, and MCH. Previous studies have demonstrated a significant influence of hematological parameters in diabetes-related microvascular complications, including neuropathy, retinopathy, and nephropathy.[23] The relationship between HbA1c fluctuation and DPN in people with T2DM has been amply supported by several studies. As a result, it has gained recognition as a robust biomarker for DN in these individuals.[10] Our results demonstrated elevated levels of lymphocytes in both groups of the study, which indicates a constant state of inflammation in the body. T2DMN patients who have HbA1c levels above 8% show significantly higher LYMPH and NLR values compared to T2DM patients, indicating a higher risk of DPN complications.[24] The close correlation between HbA1c levels and DPN in T2DM suggests that HbA1c variability could be used as an indicator for DPN.[10] Several studies and findings also highlight the relationship between elevated HbA1C and platelet dysfunction in individuals with T2DM, which is important to discuss as it can lead to T2DM-related complications such as T2DM leads to platelet hyperactivation, causing increased aggregation and potential cardiovascular complications.[25,26] This can result in inflammation linked to insulin resistance and elevated HbA1c levels. Higher platelet counts are associated with poor glucose control and higher HbA1c levels, which can contribute to thrombosis and inflammation.[26,27] Studies show positive correlations between platelet count, HbA1c levels, fasting blood glucose, and high sensitivity C-reactive protein levels. Platelets play a crucial role in coagulation, but hyperactivation in T2DM patients can lead to cardiovascular complications and diabetes-associated angiopathies.[13,28] This hyperactivation is influenced by alterations in signal pathways and decreased insulin receptor sensitivity.[13] The mechanisms contributing to altered platelet behavior include enhanced reactive oxygen species, abnormal intracellular calcium homeostasis, and nitric oxide bioavailability, resulting in the release of proinflammatory cytokines.[29] Higher platelet levels are a risk factor for thrombosis and inflammation, and abnormal platelet morphology can increase the risk of vascular problems. Research has shown that increased platelet counts correlate positively with poor glucose and HbA1c.[30] Lippi et al found a connection between platelet count and HbA1c, and another study found that platelet count is significantly associated with HbA1c and is a crucial indicator of thrombotic potential in microvascular complications. Xiao et al also suggested that platelet volume is linked with peripheral neuropathy complications in T2DM.[29,31]

One important finding in our study was the presence of inflammation biomarkers called NLR. Research has shown that inflammation plays a central role in DM and its related complications, often due to problems with how the body responds to insulin.[32] Inflammation can disrupt the activity of beta cells responsible for producing insulin and increase cell death. Lipocyte inflammation can also affect beta cell function, leading to harmful effects from elevated glucose and fat. These changes set off a cycle of inflammation, as the effects of excessive fat can also contribute to more inflammation in the body.[33] Also, the role of NLR as an inflammatory predictor has been confirmed in T2DM and it has been suggested to be correlated with A1c in the diabetic population.[34,35] Research also revealed that PLR and NLR have emerged as potential and new inflammatory biomarkers in systemic disorders. Increased levels of PLR and NLR have been shown in DM and DPN.[36] Onalan et al, in their study, failed to identify a link between neuropathy and NLR. However, they found a significant relationship between PLR and neuropathy.[37] Contrary to these findings, Raya et al established a relationship between NLR and diabetic patients with peripheral neuropathy compared to control subjects.[38]

Another inflammatory predictor, PLR, is increased in inflammatory situations such as thyroiditis, cancer and ulcerative colitis. Moreover, PLR is also reported to be correlated with T2DM and A1C.[39] Another study examined the association between T2DM and inflammation using the PLR. Results showed that T2DM patients had a significantly higher median PLR than healthy controls, indicating an elevated inflammatory response. PLR showed significant positive correlations with HbA1c, fasting plasma glucose, and c-reactive protein levels. The study suggests PLR could be a useful index for predicting T2DM development and control levels.[40]

Our study found a significant negative correlation between HbA1c and MCV and MCH, as well as a significant positive correlation with HB. These findings align with previous research that has demonstrated an inverse connection between HbA1c and MCV, and MCH in patients diagnosed with T2DM.[5] The results of our study imply that patients with T2DM are more prone to developing anemia. Additionally, we established a significant link between the PLT/MCH ratio and neuropathy in individuals with type 2 diabetes, highlighting the potential usefulness of this ratio in identifying the underlying factors contributing to neuropathy. In line with Beyan et al findings, our study suggests that the PLT/MCH ratio may particularly aid in identifying the causes of neuropathy in cases where both vitamin B12 deficiency and iron

deficiency anemia coexist. Moreover, the observed correlation between HbA1c and PLT/MCH further supports the notion that the ratio could serve as a screening tool for detecting vitamin B12 deficiency in patients with iron deficiency.[41]

Since all these markers are associated with inflammatory conditions and the relationship between diabetes mellitus and inflammation is complex, hematological parameters like HbA1c, platelet count, NLR, PLR and PLT/MCH ratio play a role in DN. Elevated levels are linked to increased inflammation and a higher risk of complications; these markers indicate disease progression and severity, contributing to cardiovascular problems, vascular and DM complications. Thus, their relationship with DPN can be considered reasonable.

Strengths

- The study compared hematological parameters among groups and found significant differences, aiding in understanding potential variations in T2DM and T2DMN.
- The significance level was set at 0.05, aiding the interpretation and assessment of associations. Understanding the interplay between inflammation and hematological parameters in diabetes can improve management and monitoring strategies for DN and other complications.
- Findings contribute to understanding the physiological and pathological pathways and offer novel insights into potential correlations.
- A novel technique for predicting and modelling continuous variables, Automatic Linear Modelling (ALM), is provided.
- Our findings may help in the management and treatment of T2DM patients.

Limitations

- The study design was retrospective, relying on data collected from medical records.
- The retrospective nature of this study was limited to data collected from a single center.
- The study examined the significance and generalizability of hematological markers and their correlation with HbA1c levels to comprehend T2DM and its consequences.
- However, the generalizability and statistical strength of the results may be constrained by restrictions, including missing or insufficient data and variable data collection methods.

Conclusion

This retrospective study aimed to investigate the relationship between HbA1c levels and hematological parameters in patients with T2DM and neuropathy. The results showed a significant correlation between HbA1c levels and various hematological parameters, including HB, MCV, MCH, PLT, and the PLT/MCH ratio in T2DM patients with neuropathy. Interestingly, the study also observed a positive association between HbA1c levels and age in patients without neuropathy, but a negative association in patients with neuropathy. This highlights the importance of considering age as a potential factor in the relationship between HbA1c levels and neuropathy. However, it is important to note that this was a retrospective study, and further research is needed to confirm these findings. Long-term studies that consider factors such as age and gender could provide more comprehensive insights into the relationship between HbA1c levels, hematological parameters, and neuropathy in diabetic patients.

Ethical Approval

The study of the protocol was reviewed and approved by the Biomedical Research Committee of Medical College, KAU, with study number 146-22. The Authors hereby affirm that this study has been conducted in full compliance with the principles set forth in the Declaration of Helsinki. The study design and data handling procedures along with the data confidentiality of patients were reviewed by the Biomedical Research Committee, ensuring compliance with ethical guidelines and the Declaration of Helsinki.

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The authors have no conflicts of interest to declare that are relevant to the content of this article.

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