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Comparative Assessment of Immunological, Hematological, and Serological Profiles in Type 2 Diabetic and Non-Diabetic Patients: A Matched Case-Control Study

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Abstract **-Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with systemic complications, including hematological and immunological alterations. This study aimed to assess differences in hematological and serological parameters between patients with T2DM and matched non-diabetic controls.**

A case-control study with matching was conducted between November 17, 2024, and February 2, 2025, at Smart Health Tower–Raparin, Ranya City. There were 176 participants, with 88 patients with type 2 diabetes mellitus and 88 matched healthy controls. Comparative hematological and biochemical marker measurements between the groups were made using the Mann–Whitney U test. Spearman's rank correlation was used to estimate the correlation of intercellular adhesion molecule-1 and interleukin-31 with different laboratory markers. The chi-square and Fisher tests were used to compare the frequency distribution of abnormalities in the blood film. A p-value < 0.05 was considered significant.

T2DM patients had significantly higher levels of HbA1c, fasting blood glucose, CRP, ESR, ICAM-1, IL-31, ferritin, total cholesterol, LDL, triglycerides, VLDL, and lower HDL (all $p < 0.01$). Morphological abnormalities were significantly more frequent among diabetics. IL-31 showed strong positive correlations with HbA1c ($r = 0.68$), glucose ($r = 0.56$), CRP ($r = 0.45$), and ESR ($r = 0.30$) (all $p < 0.01$). ICAM-1 was not significantly correlated with other measured parameters.

T2DM is associated with significant hematological and biochemical alterations, including elevated inflammatory markers and abnormal red cell morphology. Regular monitoring of these parameters may aid in the early detection and management of diabetes-related complications.

Keywords: Intercellular adhesion molecule-1 (ICAM-1), Interleukin-31 (IL-31), Type 2 diabetes mellitus.

I. INTRODUCTION

Diabetes mellitus is a chronic, multifactorial disease with a background feature of persistent hyperglycemia due to a defect in insulin secretion, insulin resistance, or both [1]. It can be broadly categorized into three categories: Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) [2]. Type 1 Diabetes Mellitus (T1DM) is caused by autoimmune destruction of pancreatic β-cells and requires long-term insulin therapy for survival [3]. GDM, typically detected during the second or third trimester, resolves postpartum but confers an elevated lifetime risk of T2DM for both mother and offspring [4, 5].

T2DM constitutes more than 90% of all diabetes cases and is driven by a combination of insulin resistance and progressive pancreatic β-cell dysfunction [6]. Obesity, poor diet, and physical inactivity as well as, genetic factors are strongly linked to T2DM [7]. Once considered a disease of middle-aged and older adults, T2DM is now increasingly prevalent among adolescents and young adults, a shift with major public health implications [8].

The global burden of diabetes is accelerating at an alarming rate. In 2022, an estimated 800 million individuals were living with diabetes worldwide, with projections suggesting this number may rise to 1.3 billion by 2050 [9, 10]. Most of this growth is concentrated in low- and middle-income countries. Diabetes now ranks among the leading global causes of premature mortality and disability, with a global prevalence estimated at 6.1% [11].

T2DM is associated with widespread systemic complications affecting the cardiovascular, renal, hepatic, and hematological systems [12]. Conventional monitoring of glycemic control ,typically through fasting blood glucose and glycated hemoglobin (HbA1c) captures only part of the disease spectrum[13]. Emerging evidence suggests that alterations in hematological indices, iron metabolism, inflammatory biomarkers, and immunological pathways may precede or parallel glycemic deterioration, offering additional diagnostic and prognostic value [14].

Iron homeostasis is particularly relevant in T2DM, given its role in oxygen transport, oxidative stress, and

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inflammation. One of the most complicated in diabetic type 2 mellitus patients are abnormalities in ferritin, iron, transferrin saturation, total iron-binding capacity ,and unsaturated iron-binding capacity [15-17]. Similarly, hematological derangements ,including anemia, erythrocyte morphological changes, leukocytosis, and platelet abnormalities, are increasingly recognized in individuals with diabetes, potentially reflecting chronic inflammation or organ dysfunction [18-21].

Liver enzyme abnormalities, including elevated ALT, AST, ALP, and bilirubin, are prevalent in type 2 diabetes mellitus (T2DM) and are generally reflective of background insulin resistance and non-alcoholic fatty liver disease (NAFLD). Similarly, elevated levels of creatinine, urea, and BUN are potent predictors of diabetic nephropathy, a common microvascular complication and the leading cause of chronic kidney disease (CKD) among diabetic patients [22]. Dyslipidemia, characterized by increased total cholesterol, LDL, triglycerides, VLDL, and decreased HDL, is nearly universal in poorly controlled diabetes and contributes substantially to cardiovascular morbidity and mortality [23].

Current literature assigns significant value to low-grade systemic inflammation as a factor in the pathogenesis of type 2 diabetes mellitus (T2DM). Pro-inflammatory ,such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-31 (IL-31), and intercellular adhesion molecule-1 (ICAM-1) have been associated with insulin resistance, vascular endothelial dysfunction, and the advancement of diabetic comorbid conditions [24, 25].
Despite increasing recognition of the multisystem nature of T2DM, no studies have provided an integrated analysis of hematological, immunological, biochemical, and inflammatory parameters in diabetic individuals compared with matched healthy controls in Iraq. Moreover, the potential diagnostic and prognostic significance of novel markers such as IL-31 and ICAM-1 in the diabetic population remains underexplored.

The aim of this study is to comprehensively evaluate a wide spectrum of clinical and laboratory parameters including glycemic markers (HbA1c, glucose), hematological indices (CBC, peripheral blood smear), iron metabolism markers (serum ferritin, iron, TIBC, UIBC, transferrin saturation), inflammatory biomarkers (CRP, ESR), immunological indicators (IL-31, ICAM-1), renal and hepatic function tests, lipid profiles, and anthropometric measures among patients with T2DM in comparison with matched healthy controls. Additionally, the study investigates correlations between selected inflammatory and metabolic markers to better understand their clinical utility in the early identification of complications and potential therapeutic targeting.

II. Materials and Methods

A. Study Design and Setting

This case-control comparative study with matching was designed to compare hematologic and serologic parameters in type 2 diabetes mellitus (T2DM) patients and matched controls. This study was undertaken from November 17, 2024, to February 2, 2025, at Smart Health Tower – Raparin, Ranya City, Kurdistan Region of Iraq.

B. Study Population

The research had 176 participants, 88 type 2 diabetes mellitus (T2DM) patients and 88 matched healthy controls. All participants were aged between 25 and 60 years. The inclusion criteria for the T2DM group were a documented diagnosis of diabetes with a duration of at least two years, on oral hypoglycemic agents. Diagnosis was confirmed by a specialist physician based on established clinical and laboratory criteria. Healthy controls were defined as individuals with no prior diagnosis of diabetes and with normal fasting glucose and HbA1c levels. Both groups were evenly matched by gender, with 44 males and 44 females in each group, to eliminate potential sex-related confounding.

C. Inclusion and Exclusion Criteria

Inclusion criteria for the T2DM group required a documented diagnosis of diabetes for at least two years with current pharmacological treatment. The control group included individuals with normal glycaemic indices and no history of chronic illness. Exclusion criteria for both groups were as follows: history of autoimmune disorders, current or recent use of systemic corticosteroids, alcohol dependence, pregnancy, and individuals under 25 years of age.

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D. Clinical Characterization

T2DM patients were clinically characterized by classical symptoms of hyperglycemia, including polyuria, polyphagia, polydipsia, fatigue, unintended weight loss, and blurred vision. These clinical features supported the identification of patients potentially at risk for subclinical diabetic complications. Control participants were asymptomatic, non-diabetic individuals confirmed to be free of metabolic or chronic disease through clinical evaluation and laboratory screening.

E. Specimen Collection and Processing

Venous blood (7 mL) was drawn from each participant using standard phlebotomy procedures. Of this, 3 mL was collected into gel-separator tubes for serum extraction and 2 mL into EDTA tubes for whole blood analysis, and 2 mL into a sodium citrate tube for ESR test. Serum samples were allowed to clot at room temperature for 10–15 minutes, followed by centrifugation at 5000 rpm for 15 minutes. The serum was aliquoted: one portion was used immediately for standard biochemical analysis, and the other was stored at –70°C for later immunological testing. EDTA-treated samples were used for analysis of HbA1c, CBC, and peripheral blood smears.

F. Laboratory Investigations

All laboratory tests were conducted using standardized automated analysers and validated commercial kits. Complete blood count and differential analysis were performed using the Medonic five-part differential hematology analyser (Boule Diagnostics, Sweden), while

peripheral smears were examined microscopically using an Olympus microscope (Japan). Liver function tests (AST, ALT, ALP, TSB), renal function tests (creatinine, blood urea, and BUN), lipid profile (CH, TG, LDL, HDL, and VLDL), and iron studies (iron, ferritin TIBC, UIBC, and transferrin saturation,) were measured using the Cobas 6000 and Cobas e411 analyzers (Roche Diagnostics, Germany). C-reactive protein (CRP) was quantified using Cobas 6000, while ESR was analyzed using the Smart Rate 10 automatic ESR analyzer (JOKOH, Japan) , and Romanowsky stain was used [26, 27].

G. Immunological Assays

Serum concentrations of interleukin-31 (IL-31) and intercellular adhesion molecule-1 (ICAM-1) were measured using ELISA kits (Cat. Nos: EH0197 for IL-31 and EH0161 for ICAM-1; Fine test brand). After complete thawing of stored serum, ELISA reagents were equilibrated to room temperature for 30 minutes. Serial dilutions of standard solutions were prepared for each assay. Samples and standards were analyzed using the Chromate® Microplate Reader 4300 (Awareness Technology Inc., USA), with optical densities measured at 450 nm [27].

H. Ethical Considerations

The Institutional Review Board of the University of Raparin provided ethical clearance (Reference No. 2866/28-5-2023) prior to data collection. The research adhered to the ethical principles of the Declaration of Helsinki. The participants provided written informed consent following a detailed explanation of the study's objectives, procedures, and potential risks. They were informed that they could withdraw from the study at any time and that participation in the study was a matter of choice. Confidentiality of the participants' information was fully maintained throughout the study, and the personal information of the participants was deleted to maintain the anonymity of the data prior to any statistical analysis.

I. Statistical Analysis

Statistical analysis was conducted using GraphPad Prism software, version 9.0. Continuous data were expressed as mean ± SD. Mann–Whitney U test (non-parametric) was used to analyze the type 2 diabetes mellitus (T2DM) patients and the healthy controls. Spearman's rank correlation analysis was used to evaluate potential correlations between intercellular adhesion molecule-1 (ICAM-1) interleukin-31 (IL-31) with the various hematological and biochemical markers. The chi-square test and Fisher's exact test were used to compare the frequency distribution of abnormalities in blood film between T2DM and HC. A p-value of below 0.05 was utilized to establish statistical significance.

III. RESULTS

A. Demographic and Anthropometric Characteristics

The study included 176 participants (88 T2DM and 88 HC) with equal gender distribution (44 males and 44 females per group). The mean age was significantly higher in the T2DM group compared to healthy controls (55.55 ± 0.70 vs. 36.00 ± 5.65 years; $p = 0.0148$). Although the T2DM group had a higher average BMI (30.80 ± 5.88 kg/m²) than the control group (25.48 ± 5.26 kg/m²), no statistical significance ($p = 0.1574$) (**Table 1**).

Table 1: Demographic and anthropometric characteristics of the T2DM and HC.

Parameters	T2DM (No=88)	HC (No=88)	P-value
Gender (M/F)	44/44	44/44	.
Age (yr) (Mean ±SD)	55.55±0.70	36±5.65	0.0148
BMI (kg/m ^{2}) (Mean ±SD)	30.80±5.88	25.48±5.26	0.1574

BMI: Body Mass Index, kg/m²: (kilograms per square meter), SD: Standard Deviation, T2DM: Type 2 Diabetes Mellitus, HC: healthy control, M: Male, F: Female. * Group comparisons were performed using the Mann–Whitney U test. P-values ≤ 0.05 were considered statistically significant.

B. Biochemical and Immuno-Inflammatory Profiles

Compared with healthy controls, individuals with T2DM demonstrated markedly elevated levels of HbA1c (7.25% vs 5.39%; $p<0.0001$) and fasting glucose (217.5 vs 97.5 mg/dL; $p<0.0001$), confirming poor glycemic control. Proinflammatory biomarkers were significantly raised, including CRP (29.97 vs 2.85 mg/L; $p<0.0001$), ESR (20 vs 4 mm/hr; $p<0.0001$), IL-31 (213.38 vs 42.09 pg/mL; $p<0.0001$), and ICAM-1 (45.87 vs 15.98 pg/mL; $p<0.0001$), reflecting an activated inflammatory and immunologic state (**Table 2) (Figure 1).**

Lipid profiles in the T2DM group showed higher concentrations of total cholesterol (216.78 vs. 162.8 mg/dL), triglycerides (179.08 vs 151.29 mg/dL), LDL (136.67 vs 112.45 mg/dL), and VLDL (35.79 vs 30.25 mg/dL), and lower HDL (34.1 vs 36.97 mg/dL), all with significant differences ($p<0.01$). Hepatic indices revealed increased AST and TSB, while ALT and ALP did not differ. Iron metabolism was disrupted, with reduced transferrin saturation (24.81% vs 29.89%; $p<0.0001$), elevated ferritin (120.59 vs 220.22 ng/mL; $p<0.0001$), and higher TIBC (414.78 vs 386.75 µg/dL; $p=0.0090$). Renal markers showed increased blood urea and BUN in T2DM, though serum creatinine remained comparable between groups **(Table 2).**

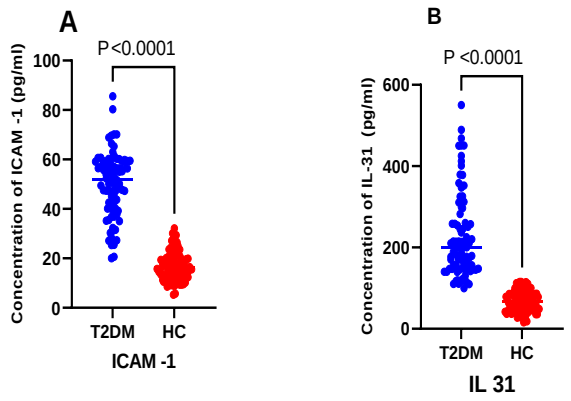

Figure 1: (A) Comparison level of Serum (A)ICAM-1 and (B) IL-31 Concentrations in T2DM and HC.

Table 2: Comparison of all biochemical tests between T2DM and HC.

Parameters	T2D(No=88) (mean ± SD)	HC (No=88) (mean ± SD)	P-value
Age (yr)	55.55±0.70	36±5.65	0.0148
BMI (kg/m 2)	30.80±5.88	25.48±5.26	0.1574
HbA1c (%)	7.25±0.18	5.39±0.11	<0.0001
ICAM -1 (pg/ml)	45.87±20.83	15.98±0.68	<0.0001
IL-31 (pg/ml)	213.38±96.2	42.09±9.39	<0.0001
CRP Titer (mg/L)	29.97±34.4	2.85±1.97	<0.0001
Glucose (mg/dL)	217.5±54.44	97.5±10.60	<0.0001
AST(IU/L)	27.88±9.07	22.2±7.77	0.0038
ALT (IU/L)	28.86± 15.04	31.3±3.53	0.7237
ALP (IU/L)	69.89±35.51	96.6±20.64	0.4681
TSB (mg/dL)	0.675±0.31	0.3±0.035	0.0035
ESR (mm/hr)	20±16.97	4±4.24	<0.0001
S. Iron (µg/dL)	101.15±20.42	116.89±50.35	<0.0001
Ferritin (ng/ml)	120.59±42.01	220.22±137	<0.0001
UIBC (µg/dL)	313.87±28.1	269.85±27.27	0.7959
TIBC(µg/dL)	414.78±8.01	386.75±23.07	0.0090
Transferrin saturation (%)	24.81±4.92	29.89±11.23	<0.0001
Cholesterol (mg/dL)	216.78±40.41	162.8±14.42	<0.0001
Triglyceride(mg/dL)	179.08±156.1	151.29±12.71	<0.0001
HDL (mg/dL)	34.1±1.97	36.97±6.96	0.0014
LDL (mg/dL)	136.67±28.52	112.45±3.04	<0.0001
VLDL (mg/dL)	35.79±31.24	30.25±2.53	<0.0001
Blood urea(mg/dL)	31.39±11.46	35.77±4.99	0.0072
Creatinine(mg/dL)	0.77±0.33	0.695±0.021	0.5762
Blood urea ntrogen (mg/dL)	14.69±5.40	16.71±2.33	0.0079

HDL: (High-Density Lipoprotein), LDL :(Low-Density Lipoprotein, VLDL (mg/dL): (Very-Low-Density Lipoprotein), UIBC: (Unsaturated Iron-Binding Capacity), TIBC:(Total Iron-Binding Capacity), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total serum bilirubin (TSB), CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, mm/hr.: millimeters per hour, HbA1c: Glycated Hemoglobin A1c, ICAM-1: intercellular adhesion molecule 1, IL-31: Interleukin-31, BMI: Body Mass Index, kg/m²: (kilograms per square meter)SD: Standard Deviation, T2DM: Type 2 Diabetes Mellitus, HC: Healthy control.* Group comparisons were performed using the Mann–Whitney U test. P-values ≤ 0.05 were considered statistically significant.

C. Hematological Profiles

Significant alterations in hematological indices were observed in patients with type 2 diabetes mellitus compared to healthy controls. Total white blood cell counts were markedly elevated in the T2DM group (8.91×10^9/L vs 6.95×10^9/L; $p = 0.0002$), reflecting potential chronic inflammation. Eosinophil counts were also significantly higher (0.18×10^9/L vs 0.03×10^9/L; $p = 0.0030$), while basophil percentage was elevated in diabetics ($p < 0.0001$). Although neutrophil and lymphocyte values did not differ significantly in absolute terms, monocyte percentage showed a marginal but statistically significant difference ($p = 0.0478$).

Red blood cell parameters revealed reduced hemoglobin (13.83 vs 15.68 g/dL; $p < 0.0001$) and hematocrit levels (43.55% vs 48.1%; $p < 0.0001$) in T2DM. Red cell distribution indices were also significantly altered, with increased RDW-CV and decreased MCHC in the diabetic group (both $p < 0.0001$). MCV and MCH values were slightly lower in T2DM, but within normal physiological limits. Platelet indices, including PLT, PDW, MPV, and P-LCR, showed no significant differences between groups (**Table 3).**

Table 3: Comparison of all hematological tests between T2DM and HC

Parameters	T2DM (No=88) (Mean ±SD)	HC(No=88) (Mean ±SD)	P-value
WBC (10^9/1)	8.905±6.31	6.95±1.48	0.0002
Neu (%)	64.65±21.99	54.06±1.32	0.6995
Neu (10^9/1)	5.32±3.50	4.24±0.084	0.6649
LYM(10^3/ML)	1.715±0.30	2.5±0.70	0.4770
Lym (%)	25.1±11.73	37.44±0.19	0.2532
Mon (10^9/1)	0.35±0.388	0.258±0.25	0.9559
Mon (%)	6.05±6.85	6.15±2.89	0.0478
Eos (10^9/1)	0.18±0.20	0.03±0.014	0.0030
Eos (%)	3.5±3.11	1.8±2.4	0.0662
Bas (10^9/1)	0.07±0.028	0.08	0.1626
Bas (%)	0.7±0.28	0.55±0.63	<0.0001
RBC (10^12/1)	5.46±0.86	5.76±0.16	0.4818
HGB(g/dl)	13.825±0.8	15.68±1.13	<0.0001
HCT (%)	43.55±2.89	48.1±1.27	<0.0001
MCV (f1)	89.55±6.15	90.6±3.67	0.0005
MCH (pg)	29.1±0.84	29.65±0.21	0.0281
MCHC (g/L)	31.05±0.77	32.05±2.05	<0.0001
RDW-SD(f1)	43.85±0.49	56±3.11	0.0122
RDW-CV (%)	12.3±0.42	11.55±0.35	<0.0001
PLT (10^9/1)	221.5±20.5	247.5±58.6	0.1399
PCT (10^9/1)	0.21±0.03	0.24±0.014	0.8126
MPV(f1)	9.8±0.56	9.5±0.84	0.1124
PDW(f1)	12.8±0.56	13.8±2.26	0.1773
P-LCR (%)	37.07±4.49	41.7±2.12	0.3728

WBC: (White Blood Cells), Neu (%) (Neutrophils - Percentage), Neu (10^9/L) (Neutrophils - Absolute Count), LYM (10^9/L) (Lymphocytes - Absolute Count), LYM (%) (Lymphocytes - Percentage), Mon (10^9/L) (Monocytes - Absolute Count), Mon (%) (Monocytes - Percentage), Eos (10^9/L) (Eosinophils - Absolute Count)Eos (%) (Eosinophils - Percentage), Bas (10^9/L) (Basophils - Absolute Count), Bas (%) (Basophils - Percentage), SD: Standard Deviation, T2DM: Type 2 Diabetes Mellitus, HC: Healthy control. RBC:(Red Blood cell) HGB: (Hemoglobin), HCT: (Hematocrit), MCV: (Mean Corpuscular Volume), MCH: (Mean Corpuscular Hemoglobin), MCHC: (Mean Corpuscular Hemoglobin Concentration), RDW-SD: (Red Cell Distribution Width - Standard Deviation), RDW-CV: (Red Cell Distribution Width - Coefficient of Variation), PLT (Platelet), PCT (Plateletcrit, %), MPV (Mean Platelet Volume), PDW (Platelet Distribution Width, FL), P-LCR (Platelet Large Cell Ratio %), f1(femtoliters), Standard Deviation, T2DM: Type 2 Diabetes Mellitus, HC: Healthy control.* Group comparisons were performed using the Mann–Whitney U test. P-values ≤ 0.05 were considered statistically significant.

D. Red Blood Cell Morphology Abnormalities in T2DM and Healthy Controls

Significant alterations in red blood cell morphology were observed in patients with type 2 diabetes mellitus compared to healthy controls. Poikilocytosis was markedly more prevalent in the T2DM group (36.36% vs. 10.22%; $p < 0.0001$). Similarly, acanthocytes (burr cells) and general acanthocytosis were significantly elevated among T2DM patients (33.0% vs. 10.22%, $p = 0.0004$; and 38.6% vs. 10.2%, $p < 0.0001$, respectively). Anisocytosis and target cells were also substantially more frequent in T2DM (40.9% vs. 13.6%, $p < 0.0001$; 32.95% vs. 5.7%, $p < 0.0001$). Tear-drop cells and spherocytes showed similar trends (39.77% vs. 9.1%, $p < 0.0001$; 20.5% vs. 3.4%, $p = 0.0007$). Microcytosis was significantly increased in T2DM (30.7% vs. 2.3%; $p < 0.0001$). In contrast, polychromasia, macrocytosis, rouleaux formation, and hyperchromia did not differ significantly between groups. Notably, hyper segmented neutrophils were markedly elevated in T2DM patients (53.4% vs. 4.5%; $p < 0.0001$) **(Table 4) (Figure 2**).

Table 4: Different abnormalities in red blood cell morphology.

RBC Morphology Abnormality	T2D(No=88)	HC(No=88)	P-value
Poikilocytosis	32 (36.36%)	9 (10.22%)	<0.0001
Acanthocytes (Burr Cells)	29 (33.0%)	9 (10.22%)	0.0004
Anisocytosis	36 (40.9%)	12 (13.6%)	<0.0001
Acanthocytes	34 (38.6%)	9 (10.2%)	<0.0001
Target Cells	29 (32.95%)	5 (5.7%)	<0.0001
Spherocytes	18 (20.5%)	3 (3.4%)	0.0007
Tear Drop	35 (39.77%)	8 (9.1%)	<0.0001
Polychromasia	1 (1.1%)	0 (0.0%)	>0.9999
Microcytosis	27 (30.7%)	2 (2.3%)	<0.0001
Macrocytosis	2 (2.3%)	3 (3.4%)	>0.9999
Rouleaux Formation	3 (3.4%)	0 (0%)	0.2457
Hyper Segmented Neutrophils	47 (53.4%)	4 (4.5%)	<0.0001
Hyperchromic	2 (2.3%)	5 (5.7%)	0.4436

T2DM: Type 2 Diabetes Mellitus; HC: Healthy Control. *P-values were calculated using the Chi-square test or Fisher's exact test, based on expected cell frequencies.

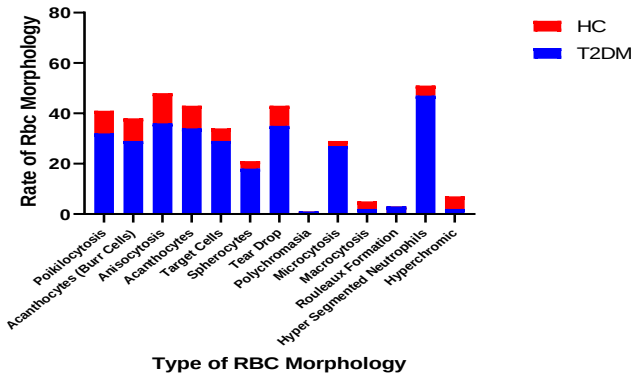

Figure 2: Different abnormal red blood cell morphology in T2DM and HC

Table 5: Correlation between Il-31 and Icam-1 with all biochemical tests

Parameter	Correlation Coefficients	IL -31	ICAM -1
ICAM -1 (pg/ml)	Rho	0.1388	.
	P-value	0.1973	.
IL -31 (pg/ml)	Rho	.	0.1710
	P-value	.	0.1111
Hba1c %	Rho	0.6767	0.0041
	P-value	<0.0001	0.9692
Glucose (mg/dL)	Rho	0.5576	-0.001
	P-value	<0.0001	0.9891
CRP (mg/L)	Rho	0.4518	0.1649
	P-value	<0.0001	0.1247
ESR (mm/hr)	Rho	0.2973	0.1554
	P-value	0.0049	0.1483
S. Iron (µg/dL)	Rho	-0.089	-0.088
	P-value	0.4068	0.4125
Ferritin (ng/ml)	Rho	0.0756	0.0198
	P-value	0.4837	0.8546
TIBC(µg/dl)	Rho	-0.018	-0.085
	P-value	0.8609	0.4278
UIBC (µg/dl)	Rho	0.0459	-0.036
	P-value	0.6707	0.7347
Transferrin Saturation %	Rho	-0.129	-0.038
	P-value	0.2285	0.7206
Cholesterol(mg/dL)	Rho	-0.001	0.0554
	P-value	0.9883	0.6080
Triglyceride(mg/dL)	Rho	-0.037	0.1027
	P-value	0.7311	0.3411
LDL (mg/dL)	Rho	0.0849	0.0480
	P-value	0.4311	0.6564
HDL (mg/dL)	Rho	0.0303	0.0068
	P-value	0.7788	0.9497
VLDL mg/dL	Rho	-0.006	0.1107
	P-value	0.9485	0.3045
Creatinine (mg/dL)	Rho	-0.039	0.1159
	P-value	0.7123	0.2821
Blood urea (mg/dL)	Rho	0.0415	0.1731
	P-value	0.7005	0.1068
Blood Urea Nitrogen (mg/dL)	Rho	0.0384	0.1806
	P-value	0.7221	0.0923
AST (IU/L)	Rho	0.1571	0.1009
	P-value	0.1439	0.3496
ALT(IU/L)	Rho	0.0124	0.1177
	P-value	0.9084	0.2747
ALP (IU/L)	Rho	0.1494	0.2728
	P-value	0.1648	0.0101
TSB (mg/dl)	Rho	0.2247	0.0780
	P-value	0.0353	0.4699
BMI (kg/m 2)	Rho	0.0369	-0.072
	P-value	0.7326	0.5025

HDL: (High-Density Lipoprotein), LDL :(Low-Density Lipoprotein), VLDL (mg/dL): (Very-Low-Density Lipoprotein), UIBC: (Unsaturated Iron-Binding Capacity), TIBC:(Total Iron-Binding Capacity), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total serum bilirubin (TSB), CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, mm/hr: millimeters per hour, HbA1c: Glycated Hemoglobin A1c, ICAM-1: intercellular adhesion molecule 1, IL-

31: Interleukin-31, BMI: Body Mass Index, kg/m²: (kilograms per square meter)SD: Standard Deviation, T2DM: Type 2 Diabetes Mellitus, HC: Healthy control. * Spearman's rank correlation coefficient (ρ) was used to assess the relationship between variables. P-values ≤ 0.05 were considered statistically significant

E. Correlation of IL-31 and ICAM-1 with biochemical parameters

A robust positive correlation was observed between IL-31 and key indicators of glycemic and inflammatory status, including HbA1c (Rho = 0.6767, p < 0.0001), serum glucose (Rho = 0.5576, p < 0.0001), and CRP (Rho = 0.4518, p < 0.0001). IL-31 was also moderately associated with ESR (Rho = 0.2973, p = 0.0049) and TSB (Rho = 0.2247, p = 0.0353). No significant correlations were identified between IL-31 and lipid indices, iron status, or renal biomarkers **(Table 5).**

In contrast, ICAM-1 exhibited minimal associations across the biochemical spectrum. It was not significantly correlated with HbA1c (Rho = 0.0041, p = 0.9692), glucose (Rho = –0.001, p = 0.9891), or CRP (Rho = 0.1649, p = 0.1247). A modest but statistically significant association with ALP (Rho = 0.2728, p = 0.0101) was the only notable finding. The correlation between IL-31 and ICAM-1 itself did not reach statistical significance (Rho = 0.1388, p = 0.1973) **(Table 5).**

IV. Discussion

In this study, we compared and correlated immunological, biochemical, and hematological parameters between patients with type 2 diabetes mellitus (T2DM) and healthy controls (HC). Our findings revealed significant alterations across multiple systems, indicating the systemic nature of T2DM.

A key observation was the significantly elevated levels of interleukin-31 (IL-31) in T2DM patients compared to healthy controls, corroborating previous reports that associate IL-31 with chronic inflammatory conditions [28]. This elevation supports the hypothesis that IL-31 may contribute to the inflammatory milieu observed in T2DM. Similarly, intercellular adhesion molecule-1 (ICAM-1) was markedly elevated in T2DM patients, consistent with earlier studies suggesting endothelial activation and vascular inflammation in diabetes [28-32].

Inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate, were also significantly increased in the diabetic group. This aligns with existing evidence that associates T2DM with chronic low-grade inflammation, likely due to persistent hyperglycemia and oxidative stress, which may predispose patients to infections and cardiovascular events [33, 34].

In terms of renal function, serum creatinine was slightly higher in the T2DM group, although not statistically significant, while blood urea and blood urea nitrogen (BUN) were significantly elevated, suggesting early renal impairment. This may reflect diabetic nephropathy, a known microvascular complication of poorly controlled diabetes, and is somewhat inconsistent with earlier findings, warranting further investigation [35].

Hepatic enzyme levels were also significantly elevated among diabetic participants, consistent with prior studies linking T2DM to hepatic and resistance to insulin and non-alcoholic fatty liver disease (NAFLD) [36].

The iron profile revealed significant reductions in ferritin, iron, transferrin saturation, and total iron-binding capacity, with unchanged unsaturated iron-binding capacity (UIBC). These findings suggest impaired iron metabolism, potentially due to chronic inflammation, increased urinary iron loss, or nutritional deficiencies [37]. Interestingly, the reduced ferritin levels contrast with some literature associating elevated ferritin with insulin resistance, but are in line with studies indicating low ferritin in cases of poorly controlled diabetes [38, 39].

Regarding lipid profiles, diabetic patients displayed a classic atherogenic dyslipidemia pattern characterized by increased total cholesterol (TCH), LDL-C, VLDL, and triglycerides (TG), alongside significantly lower HDL-C. These changes underscore insulin resistance–mediated dyslipidemia and emphasize the heightened cardiovascular risk in this population [40, 41]. The broad standard deviations observed in triglyceride and VLDL levels may reflect individual variability in glycemic control, genetic predisposition, and pharmacological interventions.

The peripheral blood smear revealed a high prevalence of red blood cell morphological abnormalities in the T2DM group, such as poikilocytosis (36.36% vs. 10.22%), anisocytosis (40.9% vs. 13.6%), and target cells (32.95% vs. 5.7%), all with p-values <0.0001. These abnormalities point to disturbed erythropoiesis or membrane remodeling, possibly driven by chronic inflammation and oxidative stress. The high frequency of spherocytes and microcytosis may reflect concomitant anemia due to chronic disease or iron-deficiency anemia. Burr cells (acanthocytes) and hyper segmented neutrophils were also notably more frequent in T2DM patients, potentially indicating folate or B12 deficiency, or generalized metabolic stress [42-44].

Other abnormalities such as polychromasia, macrocytosis, and hyperchromic cells did not significantly differ between the T2DM and HC groups. Nevertheless, these smear findings reinforce the utility of peripheral blood examination in the diagnostic and prognostic workup of diabetes.

Leukocyte profiling revealed increased absolute eosinophil counts and basophil percentages in T2DM patients, which, although less commonly studied, may implicate Th2-mediated pathways or underlying atopic tendencies in diabetic inflammation [45].

Hematological indices demonstrated that T2DM patients had significantly lower hemoglobin (HGB), hematocrit

(HCT), MCV, MCH, and MCHC values, suggesting the presence of normocytic or microcytic anemia likely secondary to chronic inflammation or renal involvement. Interestingly, RDW-CV was elevated, indicating anisocytosis, while RDW-SD was paradoxically lower. Red blood cell count remained statistically unchanged, highlighting that erythrocyte morphology is more affected than absolute cell numbers in diabetes [46].

Furthermore, we observed significant positive correlations between IL-31 and key clinical parameters such as HbA1c, glucose, CRP, and ESR, reinforcing its potential role as a pro-inflammatory cytokine in glycemic and inflammatory dysregulation [47]. However, the absence of associations with several hematological indices suggests IL-31 may act via specific pathways, emphasizing the need for mechanistic studies.

A. Limitations

This case-control study has many limitations that should be considered when interpreting the findings. First, as with all observational case-control designs, causality cannot be established—only associations can be inferred. Second, selection bias is a potential concern, particularly in the recruitment of control participants, who may not fully represent the general population without diabetes. Third, recall bias and unmeasured confounding factors (such as lifestyle, diet, duration and severity of diabetes, and medication adherence) may have influenced the observed differences between cases and controls. Fourth, although matching or adjustment was attempted, residual confounding by age, sex, or comorbidities may still exist. Additionally, the study did not stratify patients by duration of diabetes or degree of glycemic control, which could affect immunological and hematological parameters.

Finally, biomarkers such as IL-31 and ICAM-1 are affected by various inflammatory and metabolic states Whole their elevation in T2DM is noteworthy, the study design does not allow determination of whether they are causative or merely reflective of disease status. Future longitudinal or interventional studies are necessary to better understand the temporal and mechanistic roles of these biomarkers in the pathogenesis and progression of type 2 diabetes mellitus

V. Conclusion

This study demonstrates significant biochemical, hematological, and immunological alterations in patients with type 2 diabetes mellitus compared to healthy controls. Notably, elevated expression of IL-31 and ICAM-1 in T2DM suggests an amplified pro-inflammatory state. Additionally, marked abnormalities in red blood cell (RBC) morphology, increased white blood cell (WBC) counts, reduced hemoglobin levels, and altered red cell indices point to underlying subclinical inflammation, oxidative stress, and early-stage anemia in diabetic individuals. These findings emphasize the systemic nature of T2DM and underscore the potential value of routine hematological assessments, including peripheral blood smear and complete blood count, as adjunct tools for monitoring disease progression and detecting early complications.

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Conflicts of interest

The authors declare that they have no personal or financial interests or relationships that could be considered potential conflicts of interest, which that may influence the results or interpretation of the present study.

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Contributions of the authors

All authors were involved in research design and conduct, analysis of results, and manuscript writing, and approved the final version.

Ethical Authorization and Informed Consent

University of Raparin Institutional Review Board gave moral approval for conducting this study (Reference No. 2866/28-5-2023). Informed written consent was given to all the participants prior to engaging them in the research, following ethical research practices.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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