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# Role of hematological parameters in pathogenesis of diabetes mellitus: A review of the literature

Rafaqat S *et al.* Role of hematological parameters in DM pathogenesis

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**Abstract**

Diabetes mellitus (DM) is characterized by hyperglycemia and abnormalities in insulin secretion and activity. There are numerous hematological parameters; however, this review article only focuses on red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, which play an essential role in the pathogenesis of DM. Also, this review article aims to report the relationship between these hematological parameters and the development of DM. In conclusion, this article shows that increased levels of platelets, red blood cells, hematocrit, lymphocytes, eosinophils, neutrophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio and decreased levels of hemoglobin are involved in the pathogenesis of DM. However, the role of basophils in DM is unknown yet.

**Key Words:** Hematological parameters; Diabetes mellitus; Pathogenesis

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**Core Tip:** This review paper aims to determine the association between hematological parameters and diabetes with recent major advances, discoveries, significant gaps in the literature, current debates, and potential directions for future research. There are numerous hematological parameters, but this review article only focuses on red blood cells, hemoglobin, hematocrit, red blood cells indices such as mean cellular/corpuscular volume, mean cellular/corpuscular hemoglobin, mean cellular/corpuscular hemoglobin concentration, and red cell distribution width, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, which play a pathophysiological role in different types of diabetes mellitus.

## INTRODUCTION

Diabetes mellitus (DM) is a series of metabolic diseases that is characterized by hyperglycemia and abnormalities in insulin secretion and activity. Diabetes has been classified into several forms such as type 1 DM (T1DM), type 2 DM (T2DM), gestational diabetes, and other diabetes subtypes are maturity-onset of diabetes in young people and latent autoimmune diabetes in adults. The risk factors for diabetes include heredity, obesity, physical inactivity, poor diet, stress, urbanization, impaired glucose tolerance, and hypertension. Patients with diabetes who have chronic hyperglycemia have a higher risk of long-term damage to and dysfunction of many organs, especially the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy), heart (cardiovasculopathy), and blood vessels (vasculopathy), which ultimately lead to a variety of diabetic complications[1]. These complicated problems of diabetes affect patients' quality of life while also raising the risk of morbidity and mortality[2]. The global prevalence of diabetes in individuals over 18 years of age has climbed from 4.7% in 1980 to 9.3% (463 million) in 2019, and it is predicted to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045, according to an epidemiological survey, which found that DM is widespread around the world[2,3]. Diabetes continues to be a metabolic disease that

endures throughout life and is challenging to cure, despite advancements in medical technology and substantial research into the condition. As a result, the focus of diabetes diagnosis and treatment has shifted to minimizing the occurrence of complications, regulating the development of complications, and enhancing the quality of life[4]. In clinical practice, reference ranges for hematological and immunological parameters are frequently used to evaluate health and disease conditions. The reference ranges may also serve as crucial biomarkers for evaluating the course of a disease or a treatment's effectiveness. Depending on factors including age, gender, race, environment, and genetic background, these parameters may change[5]. The purpose of this review paper is to determine the association between hematological parameters and diabetes with regard to recent major advances and discoveries, significant gaps in the literature, current debates, and potential directions for future research. There are numerous hematological parameters, but this review article only focuses on red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, which play a pathophysiological role in DM, as explained in Figure 1. Several databases, including Google Scholar, PubMed, and Science Direct, were searched to identify the relevant literature. The investigation was completed on November 15, 2022. A few specific terms were used to search the published literature: Pathophysiology, diabetes, and hematological parameters. Comparable articles were discovered by searching through the references of the relevant articles. Clinical investigations were conducted in English. Although favoring more recent studies, we did not impose a time restriction.

***Discussion***

The following hematological parameters are considered in this paper: Red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio (Table 1).

### *Red blood cells*

Red blood cells, also known as erythrocytes, are the cells that consume the most glucose. The morphology, metabolism, and function of erythrocytes are invariably subject to several alterations when there is persistent hyperglycemia, which further influences hemorheology and microcirculation[6,7]. As they mature, erythrocytes shed all of their organelles, making them fairly unusual cells. They decrease the amount of energy consumed for the major functions that they must carry out and only conserve a small number of metabolic pathways for getting energy. Because of this, erythrocytes are extremely sensitive to any disease. In diabetic patients, glucose metabolism disorders have a significant impact on the morphological structure and physiological processes of erythrocytes. These disorders also cause inadequate microcirculation perfusion, hypoxia, and oxidative stress which promote the development of diabetic complications and lower the quality of life for diabetic patients. Because erythrocytes play a significant role in the pathological development of diabetic complications, the relevant erythrocyte markers also correlate with the onset and advancement of these conditions. All body tissues are affected by hyperglycemia, and the bone marrow is one of them. This result is connected to red blood cell physiology, chemical changes, and protein glycation. Alamri *et al*[8] evaluated the changes in both the pathology and regular physiology associated with chronic diabetes complications, as well as the impact of hyperglycemia on various RBC parameters. It was found that hyperglycemia had a significant impact on red blood cell count and physiological function, which could be efficiently restored with adequate glycemic control. Furthermore, Rashed *et al*[9] described that diabetic patients had significantly increased mean red blood cell count, hemoglobin concentration, and hematocrit values. Red blood cell lifespan was shortened by the low level of HbA1c, which was influenced by red blood cell characteristics and decreased in patients with hyperglycemia. As a result, red blood cell characteristics are an appropriate tool for assessing diabetes patients. Moreover, endothelial dysfunction is a novel risk factor for type 2 DM (T2DM), but it is unknown

how much erythrocytes affect the availability of nitric oxide. In the same context, Vilahur *et al*[10] suggested that red blood cells in T2DM patients need to be monitored. Although there have been many advances in the study of diabetes, the prevention and management of its consequences continue to be significant public health issues. Wang *et al*[11] concluded that erythrocyte-related indicators could offer more clinical data and could be used to track the development of diabetes and associated complications as red blood cells could sense blood glucose changes early and continually.

***Hemoglobin***

Hemoglobin is a metalloprotein that carries oxygen and is primarily found in red blood cells. Hemoglobin level is expressed as the amount of hemoglobin in grams per deciliter of whole blood. The levels of hemoglobin should be between 14 to 18 g/dL in adult men, and between 12 and 16 g/dL in adult women[12]. In addition to its role as an oxygen carrier, hemoglobin serves as an antioxidant and an iron metabolism regulator in tissues[13]. The dysfunction of hemoglobin leads to a pathological condition. Anemia symptoms are caused by a decrease in hemoglobin, whether or not there is an absolute reduction in red blood cells. Whereas, in the case of hemolysis, the hemoglobin metabolite bilirubin contributes to related jaundice, and circulating hemoglobin might result in renal failure. Nitric oxide is primarily transported by and buffered by hemoglobin. The inverse relationship between hemoglobin levels and endothelial function in human diseases has been determined. Because anemia in these patients begins earlier than in other renal diseases, it is crucial to determine whether this link also exists in diabetic patients with stage 1 to 2 chronic kidney disease. Sonmez *et al* described that endothelial function was inversely correlated with hemoglobin levels, and proteinuria was an effect modifier of this correlation in diabetic patients with stage 1 to 2 chronic kidney disease. The main finding was that proteinuria revealed a circumstance in which hemoglobin may restrict the endothelium-mediated vaso-regulation in diabetes[14].

Patients with T2DM are at an increased risk of developing diabetic retinopathy due to anemia. Diabetes-related retinopathy may also be correlated with hemoglobin levels. According to Lee *et al*[15], high hemoglobin levels were strongly associated with a lower risk of developing diabetic retinopathy in Korean patients with T2DM. In contrast, both Rossing *et al* and Ranil *et al* demonstrated that low hemoglobin concentration in patients with DM was linked to a decrease in glomerular filtration rate. Diabetes increases a person's vulnerability to low hemoglobin levels through diabetic nephropathy and diabetic retinopathy[16,17]. In the same way, Yang *et al*[18] found that lower hemoglobin levels were linked to higher vibratory sensory thresholds and an increase in the prevalence of diabetic peripheral neuropathy. In contrast, Kwon *et al*[19] explained that there were no clear mechanisms that showed the correlation between low hemoglobin concentration and diabetes profiles. As a result, doctors need to be aware of how anemia may affect people with diabetes. Increased insulin resistance and reduced insulin output are characteristics of diabetes. The functions of glucose effectiveness and first and second phase insulin secretion have been ignored. These elements are referred to as diabetic factors. It has been demonstrated that hemoglobin is associated with insulin resistance and first-phase insulin secretion but not with second-phase insulin secretion and glucose effectiveness. Chen *et al*[20] examined the relationship between hemoglobin and functions of glucose effectiveness and first and second-phase insulin secretion, determined which one had the closest correlation to hemoglobin, and demonstrated how practically all diabetic factors for diabetes were linked to hemoglobin. The relationship between insulin resistance and hemoglobin was the closely associated in Chinese patients with diabetes.

***Hematocrit***

Hematocrit is the ratio that is calculated by the volume of red blood cells and plasma. The normal ranges of hematocrit for men are 40% to 54%, whereas for women, they are 36% to 48%. Since hematocrit is calculated using whole blood, plasma volume is necessary. Hematocrit will be higher in a patient with severe dehydration than in a

patient with normovolemia. Patients will have lower hematocrit if they are fluid-overloaded[21]. Increased blood viscosity may increase the risk of insulin resistance and T2DM by reducing the amount of glucose, insulin, and oxygen that can reach metabolically active tissues. A validated formula based on baseline total plasma proteins and hematocrit was used to assess the viscosity of whole blood. Tamariz *et al*[22] depicted that increased blood viscosity and hematocrit should have been considered as a new risk factor for insulin resistance and T2DM. Capoglu *et al*[23] reported that impaired glucose tolerance and T2DM might be independent risk factors for high hematocrit levels. In addition, Dillon reported that less sugar was present in erythrocytes than in plasma. Changes in hematocrit would have an inverse effect on the concentration of whole blood sugar, which was midway between erythrocyte and plasma levels. The author provided information on glucose tolerance in individuals with chronic diseases and anemia that needs to be understood in the context of a declining hematocrit level that artificially raises blood sugar levels[24]. Feng *et al*[25] explained that the red blood cell count times hematocrit index had a strong correlation with whether or not the body exhibits insulin resistance and inflammation under impaired fasting blood glucose, making it a possible biomarker for determining prediabetes risk. However, Natali *et al*[26] demonstrated that hematocrit was inversely correlated with small vessel endothelium-dependent dilatation in both diabetics and non-diabetics. Thus, a direct adverse influence on nitric oxide availability might also contribute to the association between high hematocrit and cardiovascular disease in addition to blood rheology.

Tripathy *et al*[27] found that the combined computation of HbA1c and hematocrit during the first trimester of pregnancy was a more sensitive and specific early screening method for gestational DM. Wu *et al*[28] revealed that HbA1c and hematocrit combined might be a valuable screening method to predict gestational DM. Teodorczyk *et al*[29] evaluated that the blood glucose monitoring technology offered precise blood glucose values that were insensitive to hematocrit values between 20% and 60%. Recent therapeutic research demonstrated that sodium-glucose cotransporter 2 inhibitors

improved cardiovascular outcomes in high-risk T2DM patients. Aberle *et al*[30] found that sodium-glucose cotransporter 2 inhibition with dapagliflozin causes a continued increase in hematocrit concentration in T2DM individuals taking long-term insulin therapy.

***Red blood cell indices***

Red blood cells have been classified into four indices including mean cellular/corpuscular volume, mean cellular/corpuscular hemoglobin, mean cellular/corpuscular hemoglobin concentration, and red cell distribution width. The mean cellular/corpuscular volume is the volume fraction of a red blood cell, which is the mean volume of all the red blood cells in a sample, calculated by dividing hematocrit by the RBC count, expressed in the unit of femtolitres (fL). The average range of mean corpuscular volume is 80 to 94 fL. Mean cellular/corpuscular hemoglobin is the average mass of hemoglobin in a single red blood cell measured in picograms (pg), computed by dividing the number of red blood cells by the total amount of hemoglobin. The average range of mean cellular/corpuscular hemoglobin is 27 to 31 pg. The average amount of hemoglobin in one liter of red blood cells is known as the mean corpuscular hemoglobin concentration, which is the average amount of hemoglobin in each red blood cell. It is calculated by dividing hemoglobin by hematocrit. The range is 31.5 to 35 g/dL normally. Red cell distribution width is a metric that assesses variance in red blood cell volume or size. Red cell distribution width for adults has reference values of 11.6%–14.6%[13]. Mean red cell volume was discovered to be considerably higher in diabetic patients. Evan *et al*[31] provided evidence that elevated mean corpuscular volume in diabetic ketoacidosis and its underlying association with elevated plasma osmolarity, represented osmotic imbalance that might lead to cerebral oedema pathogenesis during the treatment of these patients. In order to overcome this state, clinicians should have replaced fluid and insulin therapy. In addition, Muntoni *et al*[32] observed the connection between fasting plasma glucose and mean red cell volume suggesting that the increase in the mean cell

volume in insulin-dependent diabetic patients might be due to an increase in the intraerythrocytic osmolality. In the same way, Kwenda *et al*[33] detected that mean corpuscular volume was a suitable marker for the diagnosis of diabetic nephropathy in patients with T2DM and demonstrated that increased mean cell volume in diabetic nephropathy due to hemodynamic changes occurred, initiated by the leakage of albumin from glomerular capillaries, excessive release of mesangial cell matrix, glomerular basement membrane thickening, and injury to podocytes. However, Davidson *et al*[34] examined that there was no correlation between the mean red cell volume and the type of diabetes, treatment, or management by measuring the levels of random blood glucose and glycosylated hemoglobin. Red cell distribution width is significantly higher in diabetic patients than in healthy subjects, and it is especially higher in uncontrolled glycemia. Red cell distribution width is commonly considered an inflammatory marker and a measure with- considerable prognostic value for mortality in diseased and healthy populations. Xiong *et al*[35] found that higher risk and poor prognosis for diabetic nephropathy were indicated by high levels of red cell distribution width in T2D patients. Likewise, Wang *et al*[36] showed that high red cell distribution width was linked to a high likelihood of developing diabetes in Chinese individuals. Red cell distribution width, an accessible, noninvasive, and practical indicator, could be considered for inclusion in the risk assessment of high-risk groups for diabetes. In another study, Yin *et al*[37] explained that higher red cell distribution width in T2D patients was associated with a considerably lower likelihood of experiencing poor glycemic control. Red cell distribution width might be used for assessment of T2D patients that carry the risk of having poor glycemic control.

In diabetes patients, red cell distribution width could be employed as a measure of glycemic level, and had a strong connection with HbA1c[38]. Also, Jaman *et al*[39] demonstrated that the glycemic marker HbA1c was correlated with red cell volume, mean corpuscular volume, mean corpuscular hemoglobin concentration, and red cell distribution width. The findings of this study were that red cell distribution width and mean corpuscular hemoglobin concentration could be used as supplemental indicators

of decreasing glucose regulation in T2DM patients. However, Renuka *et al*[40] indicated that HbA1c showed a negative connection with red cell volume, mean corpuscular volume, and mean corpuscular hemoglobin concentration, and a favorable link with red cell distribution width. The authors found that interpretation of HbA1c readings using hematological markers including red cell volume, mean corpuscular volume, and mean corpuscular hemoglobin concentration was important to diagnose and treat pre-diabetes and diabetes. In addition, Kannan *et al*[41] found that red cell turnover indices had a major impact on an HbA1c level below 7%, and clinicians must conduct additional testing utilizing plasma glucose levels to determine whether a patient had diabetes or pre-diabetes. When determining whether a patient had diabetes or pre-diabetes, 75 gm oral glucose tolerance test should be used instead of HbA1c in patients whose red blood cell distribution width is greater than 17.

The ratio of red blood cell distribution width to albumin is a risk factor for diabetic retinopathy. The effect of red blood cell distribution width-to-albumin ratio in diabetic retinopathy in diabetic patients should be confirmed by further studies[42]. In the same way, Atalay *et al*[43] have shown that the red cell distribution width and red cell distribution width-to-mean cell volume ratio could predict and be linked with diabetic ketoacidosis. These variables, however, did not help in the prediction of hyperosmolar non-ketotic acidosis. Arkew *et al*[44] found that red blood cell parameters of T2DM patients differed statistically significantly from those of the control group. A significant inverse relationship was found between RBC parameters including red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and glycemic control. Therefore, red blood cell parameter evaluation was essential for improved management of patients with T2DM. However, Alamri *et al*[8] suggested that the presence of higher blood sugar levels elevated the number of red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Poor glycemic management had a negative correlation with red blood cell distribution width, suggesting that the longevity of red blood cells was simultaneously shortened by hyperglycemia and the

development of macro- and micro-angiopathies. Nada *et al*[45] showed that red cell distribution width measurements in diabetic hypertensive individuals following indapamide antihypertensive medication or thiazide and angiotensin receptor blocker therapy were equivalent to those of the general population.

***Platelet count***

Platelet count and mean platelet volume are indicators of thrombotic potentials and risk factors for microvascular problems in diabetics. Akinsegun *et al*[46] found that mean platelet volume was lower in diabetes cases than in controls while the mean platelet count was higher in diabetes-receiving therapy patients compared to non-diabetic controls. Both indicators were within the normal reference range in diabetes treatment-receiving patients and healthy people. T2DM is a significant risk factor for cardiovascular disease. Given that platelets contribute to atherothrombosis, which is a primary cause of cardiac events, platelet function is important to understand diabetes management. Rodriguez *et al*[47] demonstrated that platelet function measured by the aggregation to adenosine diphosphate, collagen, or epinephrine was not consistently associated with diabetes but mean platelet volume was strongly associated, indicating that future research might be focused on how mean platelet volume segments pre-diabetes and diabetes for risk prediction. According to the findings of Sterner *et al*[48], elevated platelet levels were linked to both female gender and early indications of diabetic nephropathy provided that patients with DM had elevated platelet levels that exacerbated the diabetic nephropathy prevalence. DM is a prothrombotic condition with increased platelet reactivity. Mean platelet volume measured in DM correlated with retinopathy. Jindal *et al*[49] investigated platelet indices in diabetic *vs* non-diabetic patients and compared them to determine their usefulness as predictors of complications in patients with DM. Platelet indices such as platelet distribution width differed between diabetes and controls, also in the group of diabetic patients with and without microvascular problems. The majority of individuals with diabetes complications could be classified by discriminant analysis using platelet distribution

width and mean platelet volume. DM is linked to a higher risk of cardiovascular disease. Lee *et al*[50] showed that high blood glucose levels cause neutrophils to release S100 calcium-binding protein A8/A9, which then binds to the Kupffer cells' receptor for advanced glycation end products, and increases the synthesis of thrombopoietin in the liver. Megakaryocyte proliferation and enhanced platelet production are transported by thrombopoietin. These research findings validated the significance of glycemic control and discovers potential therapeutic targets for restoring platelet numbers and function in patients with diabetes.

***White blood cells***

White blood cells are a useful indicator of the risk of DM. Kheradmand *et al*[51] examined the relationship between white blood cell count and T2DM, and found a significant relationship between them in a large-scale population-based Tabari cohort study. Additionally, Twig *et al*[52] observed that white blood cell count was an independent risk factor for diabetes prevalence among young healthy persons. White blood cell count was a significant independent risk factor for diabetes in young men. In the same way, Vozarova *et al*[53] showed that high white blood cells indicated a deterioration of insulin action and the onset of T2DM in Pima Indians. It has been suggested that chronic immune system activation leads to T2DM development. In addition, diabetes factors including insulin resistance, decreased first and second-phase insulin secretion, and glucose effectiveness, are essential for the development of T2DM observed to be more common in younger persons. Kuo *et al*[54] found that the relative order of the tightness from the highest to lowest was glucose effectiveness, insulin resistance, and first and second-phase insulin secretion, and elevated white blood cell count was significantly correlated with all four diabetes factors in Chinese young men. Obesity increases the white blood cell count, which leads to an enhanced risk of atherosclerosis. Impaired glucose tolerance is characterized by a raised white blood cell count, and T2DM macroangiopathic and microangiopathic consequences are also linked to elevated white blood cell counts. Veronelli *et al*[55] highlighted the significance of

weight loss in lowering white blood cell counts in patients with morbid obesity, regardless of whether the condition was simple or exacerbated by impaired glucose tolerance or T2DM. Furthermore, Park *et al* showed that a higher white blood cell count indicated a future event of T2DM risk in community-dwelling non-obese Korean people. White blood cell count might help to identify non-obese people who were likely to develop T2DM[56].

***Lymphocytes***

T lymphocytes play an important role in the adaptive immune system linked to the regulation of metabolism of various tissues in both healthy and disease conditions. Several studies suggested that the adaptive immune system has a significant role in the pathogenesis of diabetes, including the impact of various hormones and neurotransmitters on the maturation of central and peripheral T lymphocytes, especially in the context of the metabolic burden due to diabetes. Furthermore, the function of T-effector lymphocytes in adipose and hepatic tissues throughout diabetes mutually increases pancreatic cell stress and exacerbates the condition[57]. In a study, Wu *et al*[58] showed that the diabetic group with coronavirus disease 2019 (COVID-19) had a lower lymphocyte count, reached the minimal count more quickly, and spent more time in the hospital. The minimal lymphocyte count was adversely linked with the days spent in the hospital and the days with positive severe acute respiratory syndrome coronavirus 2 nucleic acid. Giese *et al*[59] discovered a significant increase in mitochondrial oxygen consumption rate and increased basal glycolytic activity in peripheral blood mononuclear cells from diabetic INSC94Y transgenic pigs, indicating an altered metabolic immune cell profile. This research offered additional perspectives on the molecular pathways behind dysregulation of immune cells as a result of chronic hyperglycemia. Diabetic states with poor glucose management result in increased susceptibility to infections. Otton *et al*[60] observed that the metabolism of lymphocytes taken from mesenteric lymph nodes of alloxan-induced diabetic rats changed since glucose and glutamine were crucial for lymphocyte function. In short, the alterations

observed in newly acquired cells were restored by insulin injection *in vivo* or in the culture medium. Alloxan-induced diabetes did alter lymphocyte metabolism, and this may be a key contributing factor to lymphocyte function deterioration.

***Neutrophils***

Neutrophils, the most prevalent immune cell type and the first immune cells to respond to inflammation, have a unique role in the etiology of diabetes. Neutrophils may play a crucial role in the development and maintenance of T1DM. Islet cells may be destroyed by cytotoxic substances such as degranulation products, cytokines, reactive oxygen species, and extracellular traps that are generated during the maturation or activation of neutrophils. Through cell-cell interactions with other immune and non-immune cells, these cells can trigger a diabetogenic T-cell response and accelerate the onset of T1DM. The main metabolic defect in T1DM and T2DM, persistent hyperglycemia, mediates the dysregulation of neutrophil responses to infection. Both T1DM and T2DM patients frequently experience chronic and recurring infections, which increases morbidity and mortality. The high frequency of bacterial infections in diabetes is linked to a failure of neutrophil activities, including migration, ROS production, phagocytosis, and bacterial death. In diabetes, molecular pathways have impaired neutrophil function, and their connection increases the risk of bacterial infections in diabetic patients[61]. Neutrophils have a significant role in the onset of diabetic kidney damage. Yu *et al*[62] evaluated the relationship between diabetic kidney damage in autoimmune diabetes and circulating neutrophils. The strong relationship between neutrophil counts and diabetic kidney damage in autoimmune diabetes patients suggests the prospect that neutrophil-mediated inflammation plays a role in the development of diabetic kidney damage. Moreover, Woo *et al*[63] showed that systemic factors, such as inflammatory indicators, were associated with diabetic retinopathy. Both diabetes and diabetic retinopathy had elevated systemic neutrophil counts that were related to both their existence and severity. The findings suggested a link between diabetic retinopathy and systemic subclinical inflammation, and that neutrophil-mediated inflammation might be a key

player in the etiology of diabetic retinopathy. A study by Dowey *et al*[65] suggested that neutrophil targeting was a therapeutic approach that reduces inflammation and boosts host immunity in diabetes patients to enhance infection clearance. Future research must be advanced to investigate innovative therapeutics for the reduction of morbidity and mortality of diabetes[64]. Furthermore, appropriate antineutrophil therapy can inhibit or slow the progression of autoimmune diabetes and insulitis.

***Monocytes***

Monocytes express cell surface indicators of inflammation and activation status. In a study by Valtierra *et al*[66], the effects of monocyte and macrophages on glycemic/metabolic control factors, non-obese participants, or T2D were observed. T2DM-related glycemic/metabolic control affects monocyte and monocyte-derived macrophage morphologies, providing insight toward an immune-suppressive and anti-inflammatory phenotype. The research findings of Min *et al*[67] implied that the presence of diabetes complications affected the circulating monocyte phenotype. These monocyte alterations might indicate enhanced risk of diabetes complications and may be biologically linked to diabetes. Mokgalabon *et al*[68] performed a meta-analysis and higher levels of monocyte activation were found in patients with T2DM. In a study by Kitahara *et al*[69], the metabolic activity of monocytes among diabetic patients and controls was investigated, and it was found that increasing blood sugar levels in diabetic patients were linked to the metabolic activation of monocytes. Such activation can potentially harm the diabetic host by causing cell deterioration by releasing harmful oxygen products. However, Wan *et al*[70] demonstrated that diabetic patients with decreased peripheral blood monocyte levels were linked to higher risks of diabetic retinopathy, suggesting that the recruitment and inflow of monocytes into the retina contributes to diabetic retinopathy progression. In addition, Giulietti *et al*[71] suggested that the pathophysiology of T2DM and the development of common diabetic comorbidities, primarily atherosclerosis, may be related to inflammation and the activation of the innate immune system, indicating that pro-inflammatory

characteristics of monocytes are controlled by 1,25-dihydroxyvitamin D3 in T2DM patients.

***Eosinophils***

T1DM is an autoimmune condition appearing from the death of pancreatic beta cells by T lymphocytes. A few inflammatory and autoimmune illnesses have recently been linked to the pathophysiology of cationic alpha-defensin molecules. Neuwirth *et al*[72] found transcriptional active eosinophils in diabetic patients, indicating that eosinophils may be a component of a complex innate immune cell network that is involved in diabetes pathogenesis. Eosinophils, a component of leukocytes, are crucial to maintain metabolic homeostasis, particularly in T2DM patients. Ngamal *et al*[73] measured the eosinophil count and HbA1c in T2DM patients, suggesting that higher serum HbA1c levels were associated with a higher risk of developing complications from diabetes. The authors recommended that additional research was needed to determine the relationship between eosinophil-to-lymphocyte ratio and other fasting blood glucose measurements or inflammatory markers. However, Zhu *et al*[74] concluded that an increased percentage of peripheral eosinophils was linked to a lower incidence of T2DM. The inverse relationship of eosinophil with insulin resistance was found in Chinese diabetic participants. Individuals with allergic rhinitis or asthma have a higher chance of developing atherosclerosis. In a study by Fukui *et al*[75], peripheral eosinophil count was compared to assess their associations with cardiovascular mortality and diabetic nephropathy in type 2 diabetes patients, and they concluded that microalbuminuria (degree of albumin excretion rate) in men with T2DM may be related to allergic diseases. Multiple immunological diseases have been linked to increased serum eosinophil levels. Eosinophilia has been demonstrated to be a biomarker for coronary artery disease. Babazadeh *et al*[76] studied the relationship of eosinophil counts with HbA1c in patients with diabetes and coronary artery disease. However, anticholinergic effect on cognition (AEC) was not significantly correlated with HbA1c. The authors suggested that future research should be needed to examine the

relationship between AEC as a precursor to coronary artery disease and other indicators of diabetes state or glycemic management.

***Neutrophil-to-lymphocyte ratio***

Increased neutrophil-to-lymphocyte ratio is a predictor of several cardiac and non-cardiac disorders, as well as an inflammatory biomarker. Hussain *et al*[77] evaluated the relationship between neutrophil-to-lymphocyte ratio and various levels of glycemic control in T2DM patients. The authors found increased neutrophil-to-lymphocyte ratio levels with elevated HbA1c and poor glycemic control. Higher values of neutrophil-to-lymphocyte ratio indicate worst glycemic control, and it could be employed as a disease monitoring technique when diabetes patients were being followed up. Rahar *et al*[78] found that neutrophil-to-lymphocyte ratio, a novel, basic, and relatively inexpensive marker, was a useful indicator for assessing systemic inflammation in diabetes and had a correlation with the severity of T2DM. In addition, Mertoglu *et al*[79] examined neutrophil-to-lymphocyte ratio as an accurate diagnostic marker by examining its relationships to prediabetes and T2DM. Patients with prediabetes and diabetes exhibited a marked increased level of the neutrophil-to-lymphocyte ratio. This ratio considerably declined but increased in the later stages of prediabetes and the early stages of diabetes. Values for neutrophil-to-lymphocyte ratio may be accurate predictors of prediabetes and DM. Sefil *et al*[80] examined the relationship between neutrophil-to-lymphocyte ratio and HbA1c regulation. The authors discovered elevated HbA1c with increased neutrophil-to-lymphocyte ratio in T2DM patients, suggesting that regulation of HbA1c might be significantly related to neutrophil-to-lymphocyte ratio. Diabetic retinopathy is a specific neurovascular consequence of DM. Family history is a risk factor for diabetic retinopathy that can contribute to prediction and diagnosis. Hence, Wang *et al*[81] investigated the risk factors such as inflammatory response indexes and neutrophil-to-lymphocyte ratio in diabetic retinopathy patients with or without a family history of diabetes. The authors determined indicators of the systemic inflammatory response in patients without a linked family history, indicated

that neutrophil-to-lymphocyte ratio was related to the presence of diabetic retinopathy, and supported the reclassification of diabetic retinopathy in addition to Hb. In the same way, Li *et al*[82] findings showed that greater neutrophil-to-lymphocyte ratio values were a valid biomarker for the development of diabetic retinopathy. Similarly, Jaaban *et al*[83] found that elevated neutrophil-to-lymphocyte ratio was significantly related to diabetic nephropathy, suggesting that neutrophil-to-lymphocyte ratio could be used as a risk indicator for the prediction and prognosis of diabetic nephropathy. Moreover, Rahar *et al*[78] found that neutrophil-to-lymphocyte ratio was a useful marker for assessing systemic inflammation in diabetes and had a correlation with the severity of diabetic nephropathy. Also, Klisic *et al*[84] found independent correlations between HbA1c and neutrophil-to-lymphocyte ratio indexes such as derived neutrophil-to-lymphocyte ratio and monocyte/granulocyte-to-lymphocyte ratio, and platelet-to-neutrophil ratio exceeded platelets in respect of HbA1c. The prompt detection of abnormalities in glucose homeostasis in individuals with prediabetes and overt diabetes may be largely facilitated by these novel markers. Inflammation greatly influences the origin and progression of coronary artery disease. The neutrophil-to-lymphocyte ratio, a novel inflammatory biomarker, has not been linked to clinical outcomes in coronary artery disease patients with various glycemic metabolisms after percutaneous coronary intervention. He *et al*[85] discovered how neutrophil-to-lymphocyte ratio affected individuals undergoing percutaneous coronary intervention, regardless of whether they had T2DM or not. The presence of T2DM with a higher neutrophil-to-lymphocyte ratio was linked to worse clinical outcomes in coronary artery disease patients. The risk classification of coronary artery disease patients may benefit from identifying patients with increased neutrophil-to-lymphocyte ratio and T2DM. Furthermore, Wan *et al*[86] found that the neutrophil-to-lymphocyte ratio was a cheap and simple laboratory marker that can detect systemic inflammation. Apart from diabetic retinopathy, a greater neutrophil-to-lymphocyte ratio level was linked to a higher prevalence of cardiovascular disease and diabetic kidney disease in diabetic adults. In addition, Umarani *et al*[87] found that neutrophil-to-lymphocyte ratio might be an early and

predictive marker for microvascular problems in individuals with DM. Consistently, Wang *et al*[88] found that an increased likelihood of clinically significant depression symptoms was independently linked to elevated levels of neutrophil-to-lymphocyte ratio in diabetics. To better understand the involvement of neutrophil-to-lymphocyte ratio in depression in diabetes individuals, prospective research is required. Additionally, Liu *et al*[89] found that neutrophil-to-lymphocyte ratio was an easier, quicker, and more effective diagnostic for prognosis prediction in T2DM patients with COVID-19.

***Platelet-to-lymphocyte ratio***

According to emerging research, the platelet-to-lymphocyte ratio may be a new potential indicator of the inflammatory response. A higher platelet-to-lymphocyte ratio was related to cognitive decline in T2DM patients. The platelet-to-lymphocyte ratio may facilitate the early detection of high-risk patients and offer recommendations for additional measures to prevent cognitive deterioration in T2DM patients[90]. Atak *et al*[91] found that platelet to-lymphocyte ratio, which is a low-cost and simple-to-use indicator, may help predict the onset and control levels of T2DM. Additional prospective studies are required to confirm the association between platelet-to-lymphocyte ratio and HbA1c. Elsayed *et al*[92] found that patients with T2DM might have an independent relationship between platelet-to-lymphocyte ratio and poor blood glucose control. Consequently, greater platelet-to-lymphocyte ratios were linked to diabetes complications. Diabetic retinopathy, a serious and specific neurovascular consequence of T2DM, continues to be the largest contributor to vision loss and accidental blindness in individuals aged 20 to 74 years. Studies suggested that chronic inflammation plays a significant role in the pathophysiology of diabetic retinopathy. Zeng *et al*[93] explored the relationships between the platelet-to-lymphocyte ratio and diabetic retinopathy. It had been found that platelet-to-lymphocyte ratio might be an independent risk factor for assessing diabetic retinopathy in patients with T2DM. Similarly, Jaaban *et al*[83] showed that increased platelet-to-lymphocyte ratio was significantly correlated with

diabetic nephropathy, suggesting that it could be used as a risk indicator for diabetic nephropathy prediction and prognosis. In addition, Zhang *et al*[94] found that platelet-to-lymphocyte ratio is markedly increased in diabetic foot ulcer patients and positively connected with the Wagner grade of diabetic foot ulcer, suggesting that it might serve as a useful marker for the early detection and evaluation of the severity of diabetic foot ulcer.

***Monocyte-to-lymphocyte ratio***

Inflammation plays a role in disturbed metabolic control that leads to hypoglycemia, impaired fasting glycemia, or hyperglycemia. Alfhili *et al*[95] found that elevated monocyte-to-lymphocyte ratio was correlated and associated with the risk of impaired fasting glycemia and hyperglycemia. However, comprehensive prospective cohort studies are required to determine disease onset, to explore the linkage between monocyte-to-lymphocyte ratio and fasting blood glucose, and to assess the prognostic significance of this novel marker. Diabetic retinopathy is the most prevalent consequence of T2DM and the main cause of adult blindness. Although the pathophysiology of diabetic retinopathy is not completely understood, inflammation is thought to have a key factor. The platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio may be new potential indicators of inflammatory conditions. According to the research by Yue *et al*[96], platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were greatly elevated in diabetic retinopathy patients. The authors found that the monocyte-to-lymphocyte ratio was a risk factor for diabetic retinopathy after potential contributing factors were considered. The monocyte-to-lymphocyte ratio may be clinically and pathophysiologically significant in diabetic retinopathy; however, its prediction ability is limited. In addition, Wang *et al*[97] demonstrated that the monocyte-to-lymphocyte ratio was significantly related to proliferative diabetic retinopathy in patients with T2DM. Monitoring T2DM patients may be a great opportunity to assess their monocyte-to-lymphocyte ratio. Inflammation is a key pathogenetic mechanism in diabetic kidney injury. The

identification of microalbuminuria is crucial to preventing diabetic patients from developing end-stage renal failure. Inflammation is identified by a combination of high monocyte and low lymphocyte numbers. The monocyte-to-lymphocyte ratio is used as a marker in inflammatory disorders. Kocak *et al*[98] indicated that the monocyte-to-lymphocyte ratio had a strong relationship with microalbuminuria, and could act as a predictive and efficient marker for diabetic kidney injury in diabetic patients. In addition, Wang *et al*[88] discovered that elevated monocyte-to-lymphocyte ratios were considered to be indicators of systemic immunological inflammation but were found to be an unfavorable indicator of clinical outcomes in patients with gestational DM. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio may be routinely measured, and are considered to be indicators of patient survival in renal diseases and cancer. Alsayyad *et al*[99] found that lymphocyte-to-monocyte ratio might be used as an inflammatory marker in the early and intermediate phases of diabetic nephropathy, but it was no more effective than neutrophil-to-lymphocyte ratio as a screening tool for diabetic nephropathy diagnosis. In addition, Huang *et al*[100] evaluated the monocyte-to-lymphocyte ratio as a potent independent predictor of diabetic nephropathy.

## CONCLUSION

Hematological parameters play a significant role in the progression and pathogenesis of DM. Also, major hematological parameters such as red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, play pathophysiological roles in DM. The role of basophils in diabetes has not been studied yet. Therefore, further studies are required to find the association between basophils and DM.

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