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Neutrophil-Lymphocyte ratio, Platelet-Lymphocyte ratio and Red Cell Distribution Width as Prognostic Marker for Diabetic Kidney Disease with Type II Diabetes Mellitus.

Ms. Sumaiya Waheed[1], Dr. Khaleel Ahmed Manik[2*], Dr. Mukhtar Ahmad[3]

Author details

[1] Research Scholar, Department of Physiology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, India.

[2] Professor, Department of Physiology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, India.

[3] Associate Professor, Department of Medicine, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, India.

***Corresponding author:**

Dr. Khaleel Ahmed Manik,

Professor, Department Of Physiology, Integral Institute of Medical Sciences And Research, Integral University, Lucknow, India,

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Abstract

Diabetic nephropathy/diabetic kidney disease (DKD) is a major factor contributing to renal failure. To enable prompt and effective treatment, it is critical to detect the onset or progression of diabetic nephropathy early on utilizing the right screening and diagnostic techniques. In patients who suffer from type II diabetes, inflammation is a major factor in the onset and progression of diabetic nephropathy. DKD in T2DM is recognized to exhibit an inflammatory pathology. Numerous inflammatory markers, comprising interleukin 1 (IL-1), IL6, IL-18, tumor necrosis factor-alpha, transforming growth factor-beta 1, and various cytokines, have been identified in association with diabetic kidney disease. Their use in ordinary clinical practice is limited for this purpose due to their high cost, unavailability, and challenge in standardizing the test. The total leucocyte count is a rudimentary though accessible, affordable, and sensitive measure of the level of inflammation; WBCs have a positive correlation with inflammation, especially in cardiovascular illnesses. Red blood cell volume variation is quantified by the red blood cell distribution width. An elevated neutrophil count is linked to thrombus formation and ischemic injury. Platelet–lymphocyte ratio and neutrophil–lymphocyte ratio are two of the many complete blood count parameters that have been thoroughly studied as inflammatory markers in cardiac and non-cardiac diseases; NLR has been proposed as a predictive indicator for acute myocardial infarction, heart failure, and stroke. Numerous researchers have assessed the significance of NLR, PLR, and RDW as DKD markers globally, and they have recognized these as unique surrogate markers of DKD.

Introduction

Diabetes mellitus (DM), with its increasing incidence and prevalence rates, represents a major global health problem. The number of people with diabetes worldwide reached 463 million in 2019. Based on estimates from the International Diabetes Federation (IDF), there could be 700 million cases of diabetes worldwide by 2045 [1].

DM is a chronic metabolic disease that is characterized by high glucose levels (hyperglycemia) due to impairment of insulin secretion, cellular insulin resistance, or both. There are two basic forms of diabetes: Type-1, in which the pancreas is unable to make insulin, and Type-2, in which either inadequate insulin is secreted or the body is unable to use it efficiently. Diabetes mellitus (DM) can cause serious complications like diabetic nephropathy (DN), diabetic retinopathy, and diabetic neuropathy (microvascular complications), in addition to stroke, cardiovascular diseases (CVDs), and peripheral vascular disorders (macrovascular complications) [2,3,4].

One of the main microvascular consequences of diabetes mellitus (DM) is diabetic nephropathy, which is also a major cause of end-stage renal disease (ESRD). It is widely accepted that diabetic nephropathy is a heterogeneous disorder caused by a combination of environmental and genetic factors [5,6].

One of the most frequent causes of end-stage renal disease (ESRD) is diabetic kidney disease (DKD), one of the microangiopathic consequences of diabetes mellitus. DKD

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is characterized by increased excretion of albumin in the urine [7]. Existing data suggest a potential role for the inflammation in pathogenesis of type-2 diabetes mellitus (T2DM) [8]. Prior research examining the connection between systemic inflammation and cardiovascular disease found that in people with diabetes mellitus, chronic inflammation facilitates the onset and progression of microangiopathy and macroangiopathy [9]. DKD in T2DM is known to have inflammatory pathology.

Numerous inflammatory markers such as interleukin-1 (IL1), IL6, IL8, transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), and cytokines are found to be linked to DKD. Their use in ordinary clinical practice is limited for this purpose due to their high cost, unavailability, and challenge in standardizing the test [10]. The total white blood cell count, or WBC count, is a rudimentary but accessible, affordable, and sensitive measure of the level of inflammation; WBCs have a positive correlation with inflammation, especially in cardiovascular illnesses [11]. Ischemia damage and thrombus development are linked to an increase in neutrophil counts [12] Neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) are two of the many complete blood count (CBC) parameters that have been thoroughly studied as inflammatory markers in cardiac and non-cardiac diseases; NLR has been proposed as a prognostic marker in acute myocardial infarction, heart failure, and stroke [13]. Globally, numerous researchers have assessed the significance of NLR and PLR as indicators of DKD, establishing them as innovative surrogate markers for diabetic kidney disease [14].

Red blood cell distribution width (RDW) is a measurement of the range of variation in red blood cell (RBC) volume that is also included in blood tests as part of the complete blood count (CBC). According to research results, RDW may be a helpful prognostic indicator to assess diabetic nephropathy or other diabetes-related issues [15]. A study [16] conducted a retrospective investigation that supported a prior finding in which a large sample of senior European outpatients showed a significant association with RDW and HbA1c. Additional research revealed that the RDW and RDW/MCV ratios were useful in predicting diabetic ketoacidosis (DKA) and were linked to DKA [17]. RDW has the potential to be a novel biomarker for improving diabetes risk assessment and forecasting the consequences of the disease because of its accessibility and affordability.

In light of this, we set out to investigate any potential associations between type II diabetes patients' red cell distribution width, platelet lymphocyte ratio, neutrophil-lymphocyte ratio, and diabetic kidney damage.

Epidemiology of Diabetic Kidney Disease

Chronic kidney disease (CKD) is currently most commonly caused by diabetic nephropathy. Diabetes of any type increases the risk of developing chronic kidney disease, which can lead to end-stage renal disease (ESRD). Type II diabetes is far more common than type I diabetes, and people with end-stage renal disease (ESRD) frequently have type II diabetes.

The overall incidence 20 years after diagnosis varies from 4 to 17%, and after thirty years, it rises to about 16%. Research points to a decreasing prevalence of nephropathy in people with type 1 diabetes [18]. The primary causes of this are early detection of type I diabetes and efficient management of hyperglycemia; diabetic nephropathy affects 20–30% of patients with type I and type II diabetes.

The absence of retinopathy and albuminuria confirms that about 30% of those with type II diabetes who experience kidney impairment are not suffering from diabetic nephropathy but rather other renal diseases [19].

Nephropathy develops as a steady decline after reaching its peak incidence 10 to 20 years after the onset of diabetes. Therefore, it is probable to reduce the risk of diabetic nephropathy if the patient has been ill for more than 30 years and is still normoalbuminuric [20].

Pathogenesis and patho-physiology of Diabetic kidney disease

Hyperglycemia not only induces glomerular lesions but also makes them worse. If blood sugar is strictly controlled, glomerular lesions may be avoided or, if they already occur, slowed down or stopped [21]. Indeed hyperglycemia plays a pivotal role in the development of nephropathy.

The creation of advanced glycosylated end products (AGEs) is one of the metabolic consequences of persistent hyperglycemia. A portion of the extra glucose in hyperglycemia binds to tissue proteins or amino acids in the blood, which eventually causes the formation of AGEs [22].

Certain metabolites of arachidonic acid cause oxidative stress and glomerular damage when they are activated through the TXA2 receptor (thromboxane A2) [23]. The glomerular basement membrane (GBM) thickening is the earliest histological alteration [24]. Hyalinization of the afferent and efferent arterioles is observed approximately after three to five years [25]. An increase in mesangium level is usually observed around three to five years after the diagnosis of diabetes, occasionally extending up to 15 years [26].

Glomeruli may be directly impacted by systemic blood pressure, which may exacerbate glomerular sclerosis. In

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type 1 diabetes with microalbuminuria, systemic blood pressure may start to rise, even if it remains within the normal range. Moreover, many individuals with type II diabetes often develop essential hypertension, which increases following the onset of renal lesions.

Biomarkers of diabetic kidney disease

The substantial morbidity and mortality of diabetic nephropathy linked to end-stage renal disease make it a major public health concern. It's a frequent and significant complication of uncontrolled diabetes that acts as a separate risk factor for the development of diabetic nephropathy as well as an essential signal of renal failure [27]. However, there are accuracy and reliability issues with the current methods for estimating proteinuria, such as quantitative urine protein assays and urine protein dipstick testing. Hence, there is a rising interest in discovering new markers for a more comprehensive evaluation of proteinuria in individuals with diabetic patients [28]. In this review, we discuss the potential utility of three ratios, namely neutrophil/lymphocyte ratio (NLR) Platelet–lymphocyte ratio (PLR), and red blood cell distribution width (RDW), as affordable, easily accessible, non-invasive markers for albuminuria in uncontrolled diabetic patients to detect diabetic nephropathy-related albuminuria at an early stage.

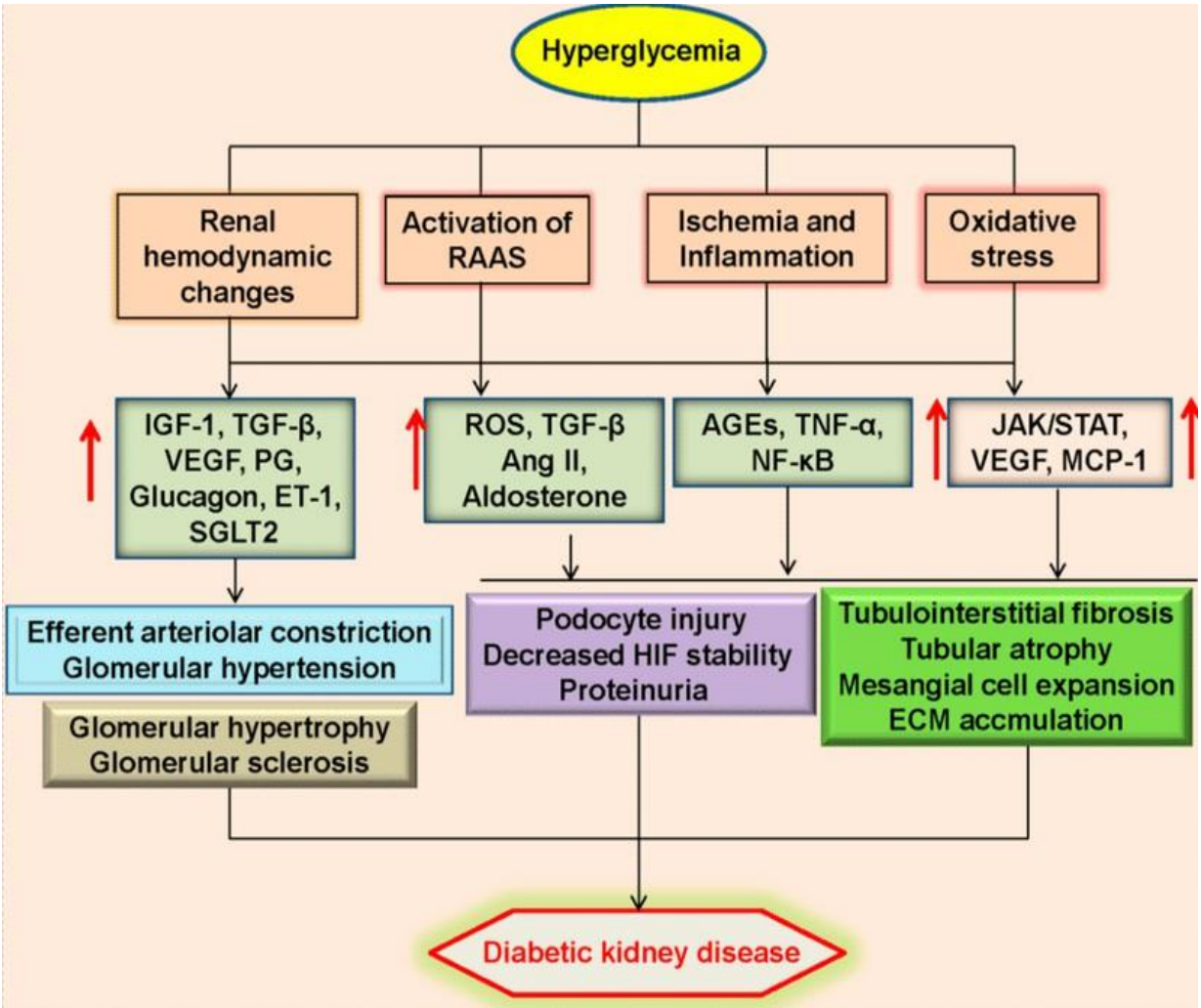

Figure 1: Conventional pathophysiology of diabetes kidney disease. Diabetic kidney disease is closely associated with renal hemodynamic changes, ischemia and glucose metabolism abnormalities, oxidative stress, inflammatory response and over-activated RAAS, which contributes to glomerular hypertension and sclerosis, tubulointerstitial fibrosis, tubular atrophy and mesangial cell expansion. RAAS, renin-angiotensin-aldosterone system; IGF-1, insulin-like growth factor 1; TGF-β1, transforming growth factor β1; VEGF, vascular endothelial growth factor; PG, prostaglandin; Ang II, angiotensin II; ET-1, endothelin-1; SGLT2, sodium glucose co-transporters 2; ROS, reactive oxygen species; AGEs, advanced glycation end products; TNF-α, tumor necrosis factor α; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; HIF, hypoxia-

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inducible factor; ECM, extracellular matrix; JAK/STAT, Janus kinase-signal transducer and activator transcription factor; MCP-1, monocyte chemotactic protein 1.

Neutrophil–lymphocyte ratio in diabetic kidney disease

The progression of diabetic nephropathy (DN) is marked by Increased urine albumin excretion signals which progresses from microalbuminuria to macroalbuminuria and finally ends in end-stage renal disease (ESRD) [29]. Currently, the diagnosis of DN relies on albuminuria as a biomarker [30]. However, renal injury commonly precedes urinary albumin secretion so its diagnostic efficacy in early-stage DN is limited [31]. Inflammation plays a crucial role in the development and progression of DN, with inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6),interleukin-8 (IL-18), and tumor necrosis factor α (TNF-α) contributing to the pathogenesis of DN [32]. However, because of their high cost and application-related technical challenges, measuring these inflammatory markers is not routinely employed in clinical practice [33].

The neutrophil-to-lymphocyte ratio (NLR) has emerged as an advanced substitute marker. Higher NLR and PLR showed a strong correlation with DN, suggesting that they could be used as prognostic risk markers and predictors of DN. Calculating these parameters in the lab is simple. NLR and PLR tests are easy to use, reasonably priced, and often conducted. They may be useful as substitute indicators of inflammation [2]. It's been suggested that NLR can serve as a stand-in marker for inflammation and endothelial dysfunction. Diabetic nephropathy is best identified and managed with early and prompt examination using low-tech diagnostic methods. In addition to albuminuria, several researchers are increasingly concentrating on early biomarkers to forecast kidney disease [34].

A series of pathological events lead to the formation and progression of diabetic nephropathy (DN), beginning with glomerular damage that results in proteinuria. This is followed by progressive renal damage, fibrosis, inflammation, and ultimately the loss of functioning nephrons. A growing body of research has shown that chronic inflammation plays a key role in the development of DM-associated complications [33]. Several studies have associated numerous inflammatory chemicals, including adipokines, chemokines, adhesion molecules, and cytokines, which may have an effect on the development of DN with chronic inflammation [35]. Therefore, it is crucial to assess the connections between the NLR level and various diabetic complications. NLR has been identified as a predictive marker for several cancer types as well as cardiovascular disorders such as heart failure, acute coronary syndromes, and coronary artery disease.

According to Wan et al [33], among diabetes people, higher NLR levels have been associated with a higher incidence of diabetes-related renal disease, cerebrovascular disorders, and cardiovascular diseases. A study [36] showed that NLR is, an independent predictor for micro-vascular complications in geriatric diabetic subjects. Another study [37] shows that NLR is a reliable and effective measure of inflammation as well as a critical predictor of the existence of microvascular diabetic complications in Egyptian patients with type II diabetes. A similar finding was quoted by Khandare et al [38] where the mean NLR was significantly higher in cases with DN than without DN. In a meta-analysis by Liu et al [37], NLR was found significant association with diabetic nephropathy severity. Dudani et al [39] reported that diabetes patients in India were found considerably greater neutrophil-lymphocyte ratio than the control group, indicating a possible role for inflammation in the development of diabetes. Wan H et al found that patients with greater levels of neutrophil-lymphocyte ratio had a relatively high prevalence of diabetic renal disease. Subramani M et al [40] did not discover a statistically significant correlation between age and NLR; however, they found that a higher percentage of DKD patients had poor glycemic control. In contrast, Khandare et al [38] reported that there was no discernible correlation between the presence or lack of DN and HbA1c. In KEEP participants with diabetes, lower eGFR and albuminuria are both independently linked to increased chances of death and ESRD progression. In this group, there is a strong synergistic relationship between a higher degree of albuminuria and a lower eGFR, which increases the risk of death and ESRD progression when both conditions are present [41].

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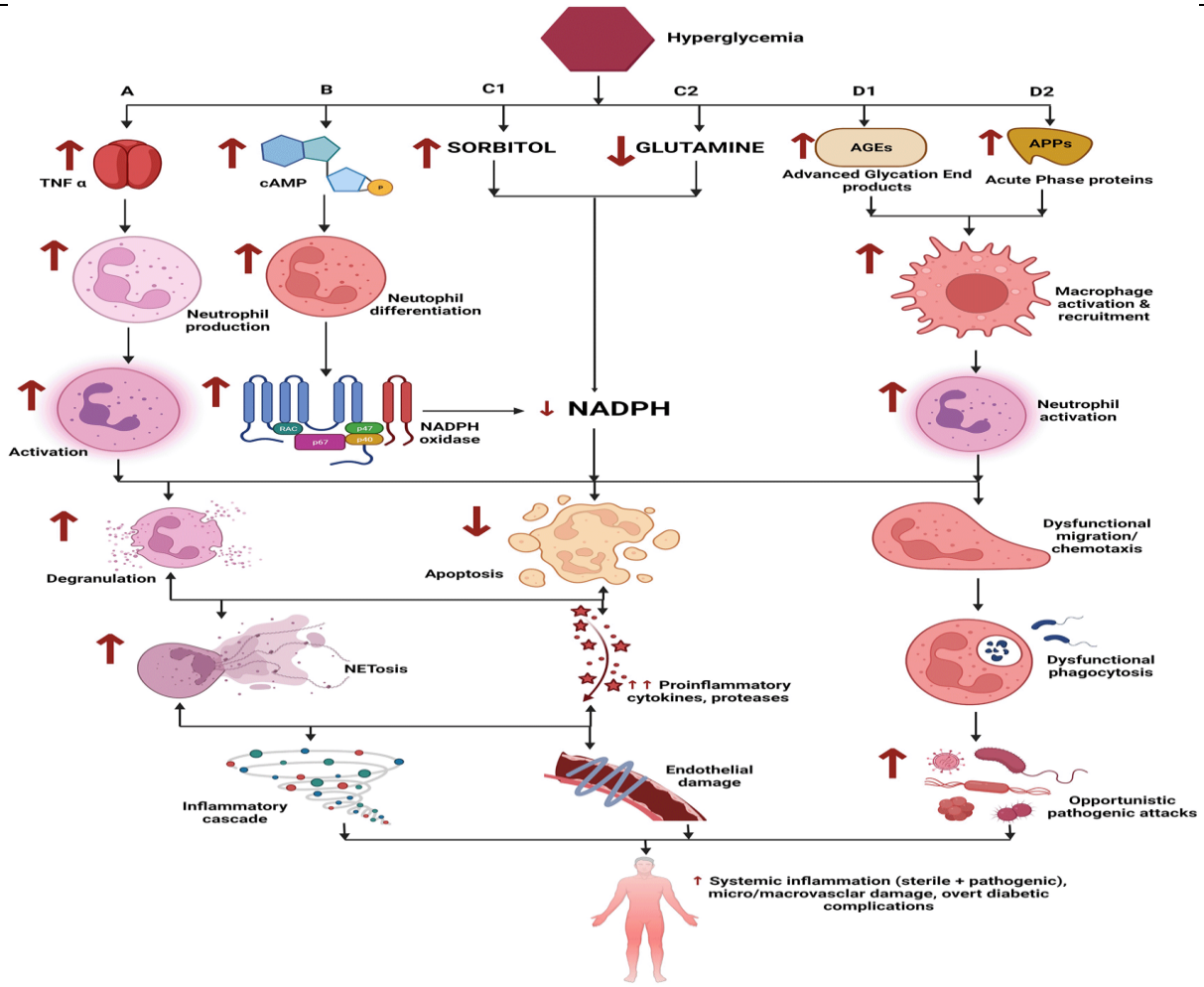

Figure 2: Role of neutrophils in Type 2 Diabetes Mellitus (T2DM).A) Hyperglycemia leads to enhanced stimulation of TNF alpha secretion which promotes neutrophil generation and subsequent neutrophil activation. B) Hyperglycemia increases intracellular cAMP which leads to increased generation of inflammatory mediators and reactive oxygen species (ROS). C1) Hyperglycemia activates the polyol pathway and leads to increased sorbitol generation. C2) Decreased glutamine has been implicated in hyperglycemia. B + C1 + C2 leads to exaggerated utilization and thus depletion of cellular NADPH. D1, D2) Hyperglycemia triggers the formation of advanced glycation end products (AGEs) and the release of acute-phase proteins (APPs) which in turn causes increased neutrophil activation. Exaggerated neutrophil activation and decreased cellular NADPH concentrations in the background of an inflammatory microenvironment, leads to dysfunctional/hyperactivated neutrophil which manifest increased degranulation, resistance to apoptosis, and dysfunctional chemotactic abilities. This cascade results in widespread systemic inflammation leading to micro and macrovascular complications of diabetes mellitus.

Platelet–lymphocyte ratio in diabetic kidney disease

A common and widely used blood test in clinical practice, the platelet-to-lymphocyte ratio (PLR) is a new biomarker that reflects the state of systemic inflammation and platelet activation. It is easily and reliably calculated [42].

According to emerging research, the platelet-to-lymphocyte ratio could be an innovative method to assess the inflammatory response. With type 2 diabetes, a greater platelet-to-lymphocyte ratio has been linked to cognitive impairment. The platelet-to-lymphocyte may make it easier to identify high-risk individuals early and provide suggestions for further steps to stop cognitive decline in T2DM patients [43]. Atak et al [44] found that the platelet-to-lymphocyte ratio is an inexpensive and easily used indication that may help predict the onset and control levels of T2DM. Additional prospective researches are required to confirm the association between PLR and HbA1c. Elsayed et al [45] found that T2DM might have an independent relationship between PLR and poor blood glucose control. Consequently, greater PLR was linked to diabetes complications.

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In our study, participants with DKD had a greater platelet count than those without DKD. Patients with diabetes who had macroalbuminuria had greater total platelet counts than those who had normoalbuminuria, similar to our findings as conducted by Fawwad et al [46] and Akbas et al [47] Similar differences in the platelet counts in DKD, and non-DKD groups observed by Kahraman et al [48] and Huang et al [49].

PLR is also a novel inflammatory bio-marker used as the prognostic factor in different diseases. Abdelaziz et al [50] observed individuals with DM who have macroalbuminuria have a greater PLR than those who have micro-albuminuria and normoalbuminuria. Akbas et al [47] and Alsayyad, and Abd Alsamie [51] also had comparable observations. The results of their investigation showed that PLR was higher in DKD patients than without DKD. On the contrary, Onalan et al [52] observed no variances in the PLR between diabetes cases with and without DKD.

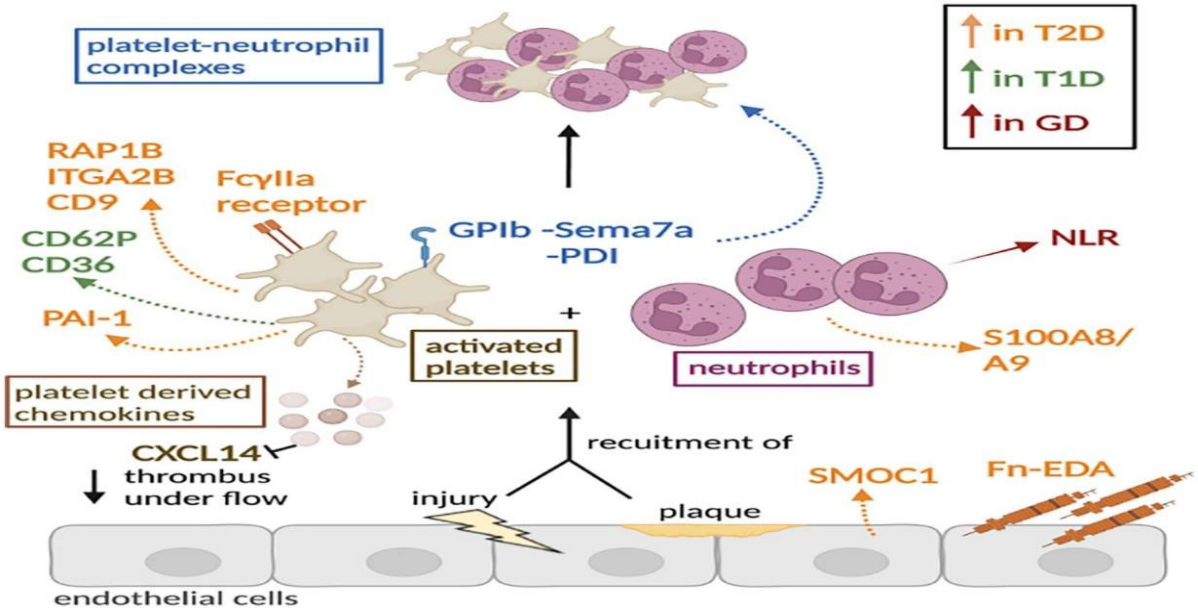

Figure 3: Cellular mechanisms involved in diabetes-associated thrombo inflammation. This figure highlights the mechanisms involved in platelet activation/aggregation and the recruitment of neutrophils that have the potential to become therapeutic targets to decrease thromboinflammation in patients with diabetes. ↑ represents an increase; ↓ represents a decrease. Increased expression of proteins is depicted in orange for type 2 diabetes (T2D), green for type 1 diabetes (T1D), and dark red for gestational diabetes (GD). Upon vessel wall injury or atherosclerotic plaque rupture, platelets are recruited to the site of injury and become activated while neutrophils scout for inflammatory signals and aggregate with amplification of response. Fn-EDA (fibronectin-splice variant containing an extra domain A) and extracellular matrix component SMOC1 (secreted modular calcium-binding protein 1) are increased in T2D. Proteins involved in platelet activation (RAP1B [Ras-related protein 1b], ITGA2B [integrin subunit alpha 2b], CD9 [CD9 antigen], and Fcγlla [Fcγ receptor type IIa]) are also upregulated in T2D. Similarly, platelet activation markers CD62P (P-selectin) and CD36 (platelet glycoprotein 4) are upregulated in T1D, suggesting that these proteins could be potential targets to decrease thromboinflammation in T2D and T1D. Other potential targets are platelet-derived chemokines, for thrombus formation under flow was shown to be decreased following the inhibition of CXCL14 (chemokine C-X-C motif ligand 14). Similarly, S100A8/A9 (S100 calcium-binding proteins A8/A9) calcium-binding proteins involved in neutrophil chemokine production and aggregation are upregulated in T2D.

Correlation of Red blood cell distribution width in diabetic kidney disease

Red Blood Cell Distribution Width (RDW) is an indicator of RBC size variability (anisocytosis) and is commonly included in the complete blood cell count [53]. Until recently, RDW has been used for the differential diagnosis of types of anemias [54] Greater RDW readings are indicative of increased RBC breakdown or decreased erythropoiesis cause, which reduces the life span of erythrocytes. Over the past ten years, Growing research has demonstrated that a high RDW is an independent predictor of cardiovascular (CV) morbidity and mortality in the

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general population, as well as in patients with acute kidney injury (AKI) treated with hemodialysis, chronic heart failure, stroke, and kidney transplant recipients [55].

Red blood cell distribution width is a measurement of the range of variation in red blood cell volume that is also included in blood tests as a part of the complete blood count (CBC). Research findings indicate that RDW may be a helpful prognostic indicator for evaluating diabetic nephropathy or other diabetes-related issues [15]. Zhang et al [16] carried out a retrospective analysis that extended the previous finding that RDW had a substantial correlation with HbA1c in a sizable group of senior European patients. Additional research revealed that the RDW and RDW/MCV ratios were useful in predicting diabetic ketoacidosis (DKA) [17]. Given its affordability and ease of use, RDW has the potential to be a novel biomarker for enhancing diabetes risk assessment and predicting complications from the disease.

Roumeliotis S et al [55] in his study compared the diabetics with normal kidney (stage 0) patients in the early stage of CKD (stages I and II) who had significantly higher RDW (13.90% vs. 14.30%). RDW increased dramatically as DKD progressed, with HD patients exhibiting the highest levels (16.25%). Even more significant is the difference in RDW between the groups when the RDW data for controls, CKD, &HD are shown separately ($p = 0.001$). Even though RDW normally ranges between 12.0% and 14.0%, they found in their study that controls' RWD was almost at the maximum (13.9%). RDW was found to be strongly correlated with proteinuria, albuminuria, and the advancement of DKD. Diabetics in the early stages of chronic kidney disease (CKD) had higher RDW than those with adequate kidney function, but RDW increased progressively as CKD stages increased. Additionally, following a 7-year follow-up period, RDW predicted the development of diabetics with CKD to ESRD. There is little information available regarding RDW and renal impairment. Large epidemiologic studies' data demonstrated a distinct, graded, and robust correlation between high RDW in the general population, and micro-albuminuria, which is consistent with our findings [56]. In a population of hypertension cases, RDW was an independent predictor of early renal impairment [57].

Banfi G et al [58], in a community-based cohort of 8585 adults showed a substantial, inverse, graded relationship between RDW and eGFR, according to their findings. The occurrence of CKD (defined as eGFR < 60 mL/min) was a significant predictor of RDW levels after controlling for gender, age, hemoglobin, and MCV. Data from the NHANES study [59], showed that compared to subjects in the lowest RDW quartile, those in the highest had more than 2-fold risk for CKD (5.20% vs 10.6, $p<0.001$). In keeping with the results, RDW was negatively connected with eGFR CKD cases stages 1–5, [60] and kidney transplant recipients [61].

Conclusion

We have attempted to briefly describe those major hematological parameters such as red blood cells, hemoglobin, red blood cell indices, platelet count, lymphocytes, neutrophils, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio play pathophysiological roles in DM. Our review established an association between NLR, PLR, and RDW and the severity of diabetic kidney disease. An increased risk of acquiring more severe types of DKD is indicated by a high RDW level. NLR rose in proportion to the rise in 24-hour urine albumin excretion. An early warning sign and predictive risk factor for diabetic nephropathy, elevated neutrophil-to-lymphocyte ratio was found to be substantially connected with the development of diabetic nephropathy. Calculating these parameters in the lab is simple. High NLR & PLR may be used as a prognostic risk marker and predictor of DN, as there was a strong correlation found between them and DN. NLR and PLR tests are easy to use, reasonably priced, and often conducted. They may be useful as substitute indicators of inflammation. This study will help in reducing the mortality rate that occurs due to DKD. Early determination of the complications and management of the cases could be done. Further studies with a prospective design and multiple NLR measurements will shed more light on the role of NLR as a marker of inflammation and probable risk factors for DN. In addition, larger studies examining should confirm these findings along with addressing the limitations of this report.

List of abbreviations:

DN: Diabetic nephropathy; DKD: Diabetic kidney disease; T2DM: Type-2 diabetes mellitus; CBC: Complete blood count; WBC: White blood cell count; NLR: Neutrophil–lymphocyte ratio; PLR: Platelet–lymphocyte ratio; RDW: Red blood cell distribution width; ESRD: End-stage renal disease; IL-1:interleukin 1; IL-6: interleukin 6; TGF-β1:Transforming growth factor-beta1; TNF-α: Tumor necrosis factor-alpha; IDF: International Diabetes Federation.

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Authors' contributions

SW, KAM and MA conceived, received, wrote, and edited the article. The authors read and approved the final manuscript.

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