ORIGINAL ARTICLE

Neutrophil–Lymphocyte Ratio and Platelet–Lymphocyte Ratio: Novel Markers in Diabetes Mellitus

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Abstract

Introduction: Diabetes mellitus (DM) is a chronic metabolic disorder with high morbidity and mortality. Neutrophil–lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have emerged as novel indicators of subclinical inflammation and can be used as potential indicators of vascular complications and poorer outcome in patients with DM. This study was conducted to evaluate the role of NLR and PLR as inflammatory biomarkers of type 2 DM.

Aim: The aim of this study is to assess NLR and PLR as predictive inflammatory markers in DM.

Materials and methods: This was a cross-sectional study carried out in Sri Siddhartha Medical College, Tumkur, from September 2018 to November 2018. The source of data included patients attending medicine outpatient department (OPD) with type 2 DM aged between 18 years and 60 years without other comorbidities. The values of glucose parameters and HbA1c were obtained from the case files. Complete blood count (CBC) was measured using the Sysmex XN 330 automatic hematology analyzer.

Results: The study was carried out on 150 diabetics and 50 subjects were used as controls. Out of 150 cases, 110 patients had well-controlled DM (HbA1c7%). Diabetic patients had a significantly higher NLR and PLR as compared to the controls ($p = 0.003$ and $p = 0.008$, respectively). Patients with poorly controlled DM had a significantly higher NLR and PLR as compared to subjects with well-controlled DM ($p = 0.02$ and 0.007).

Conclusion: Increased levels of NLR and PLR are associated with poor glycemic control. It can be used as a disease monitoring tool during the follow-up of the diabetic patients.

Clinical significance: NLR and PLR parameters are widely available, reliable, and inexpensive and are used in the prediction of diabetes-related complications in the future so that effective measures can be taken to prevent complications.

Keywords: Diabetes mellitus, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio.

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder with high morbidity and mortality.[1] Chronic inflammation plays a central role in the development and progression of diabetes and in the pathogenesis of its complications.[1]

White blood cells and their subtypes have been widely considered as inflammatory markers in various diseases, including DM.[2]

NLR represents the combination of two markers where neutrophils represent the active nonspecific inflammatory mediator initiating the first line of defense, whereas lymphocytes represent the regulatory or the protective component of inflammation.[3]

NLR and PLR are superior to other leukocyte parameters in their stability and are less influenced by physiological and pathological factors.[2]

Hence, these parameters have emerged as novel[3] indicators of subclinical inflammation and can be used as potential[4] indicators of vascular complications and poorer outcome in patients with DM.

This study was conducted to evaluate the role of NLR and PLR as inflammatory biomarkers of type 2 DM.

Aim

The aim of this study is to assess NLR and PLR as predictive inflammatory markers in DM.

Objectives

To assess the impact of DM on NLR and PLR; to compare NLR and PLR between cases and controls; and to compare NLR and PLR between subjects with well-controlled DM (HbA1c ≤ 7%) and poorly controlled DM (HbA1c > 7%).[5]

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Materials and Methods

This cross-sectional study was carried out in Sri Siddhartha Medical College and Research Centre, Tumkur, from September 2018 to November 2018. The source of data included patients attending Medicine OPD with type 2 DM aged between 18 years and 60 years without other comorbidities.

Patients with acute infections, bleeding or hematologic disorders, dyslipidemia, hypertension, smoking, heart, liver, kidney diseases, and patients on non-steroidal anti-inflammatory drugs or steroids[5] were excluded from the study.

The values of glucose parameters and HbA1c were obtained from the case files. CBC was measured using the Sysmex XN 330 automatic hematology analyzer.

The values of neutrophils, lymphocytes, and platelet count were noted and NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[5] PLR was estimated by dividing the platelet count by the absolute lymphocyte count.[6] Descriptive statistics were employed and the *p* value was calculated.

Results

The study was carried out on 150 diabetics and 50 subjects were used as controls. The age range in the diabetics was 37–69 years and, in controls, it was 33–65 years. Out of 150 diabetics, 67 cases were males and 83 cases were females. Out of 50 controls, 21 cases were males and 29 were females. The mean age in the diabetics was 44 years and, in controls, it was 40 years. The average HbA1c was 6.7% in the diabetics and 5.4% in controls. The mean fasting blood glucose in the diabetics was 146.3 mg/dL and, in controls, it was 80.1 mg/dL. The mean NLR was 2.5 and 1.02 in the cases and controls, respectively. The mean PLR was 119.7 and 95.2 in the cases and controls, respectively.

Diabetic patients had a significantly higher NLR and PLR compared to the controls ($p = 0.003$ and $p = 0.008$, respectively) as seen in Table 1.

Out of 150 cases, 110 patients had well-controlled DM (HbA1c ≤ 7%) and 40 patients had poorly controlled DM (HbA1c > 7%). The mean fasting blood glucose in poorly controlled diabetics was 166.2 mg/dL and, in well-controlled diabetics, was 147.3 mg/dL. The average HbA1c in the poorly controlled diabetics was 7.7 and, in well-controlled diabetics, it was 6.7.

The average NLR in the poorly controlled diabetics was 2.7 and, in well-controlled diabetics, it was 1.7. The average PLR in poorly controlled diabetics was 122.3 and, in well-controlled diabetics, it was 105.7. Patients with poorly controlled DM had a significantly higher NLR and PLR compared to subjects with well-controlled DM ($p = 0.02$ and 0.007) as shown in Table 2.

Discussion

DM is a component of metabolic syndrome that can result in several long-term microvascular and macrovascular complications.[2]

Several studies have confirmed the relationship between systemic inflammation and insulin resistance, in which an altered immune system plays a decisive role in the pathogenesis of DM. Although the pathophysiologic mechanisms of type 2 DM development are multifactorial, many epidemiological studies have highlighted the association of chronic low-grade inflammation with DM.

Hyperglycemia[7] increases the release of reactive oxygen species from neutrophils, which,[8] in turn, increase vascular endothelial permeability and promote leukocyte adhesion, leading to alterations in endothelial function. Deficiency in the endothelial-derived nitic oxide is also noted. Increased apoptosis in lymphocytes and its increased oxidative DNA damage contribute to its low circulating levels. The insufficient proliferation of lymphocytes due to low expression of IL-2 receptors is also noted.[9]

In contrast, hyperglycemia has been shown to reduce the apoptosis in neutrophils, leading to impaired neutrophil clearance and prolonged inflammation. Enhanced release of neutrophil proteases has also been noted in patients with type 2 DM.[8]

Nuclear factor κB (NF-κB) is induced by stimuli such as hyperglycemia and oxidative stress. The activation of NF-κB will stimulate the inflammatory response by increasing the expression of ICAM-1, proinflammatory cytokines, and chemokines. The overexpression of ICAM-1 recruits more inflammatory cells leading to persistent inflammation.

The predictive value of NLR and PLR is comparable with other inflammatory markers such as C-reactive protein (CRP), IL-1, IL-6, and TNF-α in the detection of subclinical inflammation and endothelial dysfunction.[3]

NLR and PLR increase with increasing severity of glucose intolerance.[8] NLR has been shown to be a better risk factor than total WBC count in the prediction of adverse outcomes.[8] The increased pro-oxidant activity of polymorphonuclear neutrophils has been detected in diabetics, which accelerates the vascular wall degeneration.[4]

Patients with increased NLR but normal total leukocyte count have shown to have increased risk of atherosclerosis-related diseases. HbA1c does not predict ongoing inflammation and diabetes-associated complications, which is more precisely done by NLR.[5]

Studies by Mertoglu et al. and others showed that higher values of NLR and PLR were associated with increased high insulin resistence.[1] NLR and PLR were found to be higher in the diabetic group as compared with the control group, which was similar to the findings in this study.

A study by Hussain et al. found the NLR value to be higher in the poorly controlled diabetics as compared with the well-controlled diabetics which was statistically significant (*p* value 0.001), similar to the findings in this study.[5]

Moursy et al. showed that NLR and PLR values were significantly higher in diabetic patients with retinopathy and neuropathy than those of diabetic patients without any microvascular complications.[3] Diabetic neuropathy develops as a result of hyperglycemia-induced

Table 1: Characteristics and laboratory data of diabetic patients and the controls showing the average values of the parameters

Parameters	*Controls*	*DM (150)*
Age	40	44
HbA1c	5.4	6.7
Fasting plasma glucose (mg/dL)	80.1	146.3
Neutrophils (%)	62	72
Lymphocytes (%)	30	27
Platelet count ($\times 10^5$ cells/μL)	2.4	3.1
NLR	1.02	2.5
PLR	95.2	119.7

Table 2: Statistical comparison between well-controlled and poorly controlled diabetic patients showing the mean values of the parameters

Parameters	*Well-controlled DM (HbA1c <7%) 110*	*Poorly controlled DM (HbA1c >7%) 40*
Age	45	48
HbA1c	6.7	7.7
Fasting plasma glucose (mg/dL)	147.3	166.2
Neutrophils (%)	71	75
Lymphocytes (%)	29	26
Platelet count ($\times 10^5$ cells/μL)	2.9	3.5
NLR	1.7	2.7
PLR	105.7	122.3

local metabolic, enzymatic, and microvascular changes. It has been demonstrated that endogenous TNF-α production is accelerated with microvascular permeability, hypercoagulability, and nerve damage, thus, initiating and promoting the development of characteristic lesions of diabetic polyneuropathy.

Akbas et al. associated the increased NLR and PLR values in patients with diabetic nephropathy having increased albuminuria. Verdoia et al. reported that increased NLR was related to the severity of coronary artery disease.[4] Aygun et al. found the prevalence of obstructive coronary artery disease to be higher in diabetic patients with NLR >2.05 than those with NLR <2.05. Other studies have demonstrated the link between increased NLR and poor survival after coronary artery bypass grafting, and it has been shown to be an independent predictor for major adverse cardiac events in patients with ST-segment elevation myocardial infarction.

Conclusion

NLR and PLR show a linear increase with increasing severity of glucose intolerance and have emerged as new inflammatory biomarkers of type 2 DM. NLR and PLR are widely available,[5] reliable, and inexpensive and can be used as a disease monitoring tool and in the prediction of diabetes-related complications in future so that effective measures can be taken to prevent complications.

Clinical Significance

The burden of DM is on the rise due to the strong influence of urbanization, sedentary lifestyle, nutritional, and epidemiological transition. Drastic steps are required through various health awareness programs to reduce morbidity and mortality.[5] Hence, NLR and PLR can be employed as stable prognostic risk markers of diabetes-related complications.

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