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RMASSESSMENT OF NEUTROPHIL TO LYMPHOCYTE AND PLATELET TO LYMPHOCYTES RATIO IN TYPE 2 DIABETES MELLITUS AND COMPARISON WITH HEALTHY CONTROLS

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Abstract

Introduction: Type II Diabetes mellitus (DM) is related to the insulin hormone and is seen when this hormone is incomplete or inadequate. Type II DM is a chronic disease characterized by hyperglycemia, and its incidence and serious complications have increased in recent years. Neutrophil to Lymphocyte Ratio (NLR) and Platelet-lymphocyte ratio (PLR) are important markers used in the diagnosis of general inflammatory conditions in the human body. It is stated that NLR and PLR are cheap and easily calculable markers that correlate with the prognosis of systemic inflammatory diseases and are frequently used in laboratories.

Material and Methods: This is an analytic observational and cross-sectional study with a approach to determine the difference of NLR and LMR values in patients with type 2 diabetes mellitus control and uncontrolled groups attending at Tertiary care Teaching Hospital over a period of 2 year. Laboratory examination data were taken from the Laboratory Information System (LIS), while patient demographic data, medical history, duration of illness, and drugs consumed were taken from medical record data. Furthermore, the NLR and LMR values were recorded for the NLR value obtained from the absolute neutrophils divided with absolute lymphocytes. In contrast, the LMR value was obtained from absolute lymphocytes divided by absolute monocytes.
Result: The study was carried out on 100 diabetics and 100 subjects were used as controls. The mean age in the diabetics was 51.3 ± 3.6 years and in controls, it was 61.57 ± 5.73 years. The mean Systolic Blood Pressure (mm of Hg) in the diabetics was 131.5 ± 12.7 and, in controls, it was 115.6 ± 4.98. The mean Diastolic Blood Pressure (mm of Hg) in the diabetics was 90.6 ± 12.6 and, in controls, it was 77.0 ± 4.8. The mean fasting blood glucose in the diabetics was 159.53 ± 11.83 mg/dL and, in controls, it was 86.93 ± 5.39 mg/dL. The mean Postprandial blood glucose in the diabetics was 213.1 ± 20.9 mg/dL and, in controls, it was 130.76 ± 4.51 mg/dL. The mean HbA1c was 7.69 ± 0.61% in the diabetics and 4.97 ± 0.25% in controls. The mean Platelets was 239.42 ± 69.84 in the diabetics and 4.97 ± 0.25% in controls. 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.
Conclusion: Neutrophil to lymphocyte ratio (NLR) in the uncontrolled type 2 DM group was significantly higher than in the controlled type 2 DM group. Meanwhile, the lymphocyte to monocyte ratio (LMR) did not significantly differ between the two groups. Further research that did not use secondary data is expected so the patient's body mass index, lipid profile, length of diabetes, and type of therapy can be evaluated.
Keywords: Type II Diabetes mellitus, Neutrophil to Lymphocyte (NLR), Platelet-lymphocyte ratio (PLR)

Introduction

Type II DM is related to the insulin hormone and is seen when this hormone is incomplete or inadequate. Type II DM is a chronic disease characterized by hyperglycemia, and its incidence and serious complications have increased in recent years [1]. Type II DM usually begins in humans after age 40 and is associated with obesity [2]. Leukocytes take part in our body's immune system; it consists of two cell groups, granulocytes, and agranulocytes. As a result of the joint effect of granulocytes and agranulocytes in the body, they protect living things against harmful factors and fulfill the duty of the immune system against diseases. Granulocytes consist of neutrophils, eosinophils, basophils, mast cells, dendritic cells, monocyte-macrophages and phagocytes. Lymphocytes, on the other hand, consist of natural killer cells and some specialized cells under the "T" and "B" lymphocyte groups [3].

Lymphocytes make up about half of the circulating leukocytes. The circulating life span of lymphocytes can last from a few weeks to several years, and their lifespan is considerably longer compared to neutrophils [4]. Platelets produced in the bone marrow; are essential blood elements

effective in coagulation. Platelets, besides their coagulation functions, secrete mediators against infectious agents. These mediators have been shown to coordinate inflammatory cell movements, with platelets contributing to chemotaxis and phagocytosis. [5]
In the absence or insufficiency of platelets, there is a delay in the migration of leukocytes to the inflammation region, which reveals how essential their functions are [6]. NLR and Plateletlymphocyte ratio are important markers used in the diagnosis of general inflammatory conditions in the human body [7]. It is stated that NLR and PLR are cheap and easily calculable markers that correlate with the prognosis of systemic inflammatory diseases and are frequently used in laboratories. This frequency of use can also be compared to the ratio of De-Ritis and R obtained from biochemical tests [8]. It has been reported that NLR and PLR have more common usage areas. Cardiovascular, rheumatological and cancer cases, especially inflammatory diseases, have been shown [9]. Neutrophils, lymphocytes and platelets are essential to the blood elements involved in the inflammation process. Type II DM is strongly associated with inflammation. In this study, we aimed to investigate the relationship between NLR and PLR, which are among the parameters of complete blood count and Type II DM. [10]

Material and Methods:
This is an analytic observational and cross-sectional study with an approach to determine the difference of NLR and LMR values in patients with type 2 diabetes mellitus control and uncontrolled groups attending at tertiary care Teaching Hospital over a period of 2 year.

Inclusion criteria
Type 2 diabetes mellitus patients who were at least 18 years old, did HbA1c, fasting blood glucose, and complete blood counts examination simultaneously.

Exclusion criteria
Typed 2 DM patients with complications of heart disease, chronic renal failure, infection, inflammation, hematological malignancy and pregnancy.
Laboratory examination data were taken from the Laboratory Information System (LIS), while patient demographic data, medical history, duration of illness, and drugs consumed were taken from medical record data. Furthermore, the NLR and LMR values were recorded for the NLR value obtained from the absolute neutrophils divided with absolute lymphocytes. In contrast, the LMR value was obtained from absolute lymphocytes divided by absolute monocytes.

Study participants were divided into two groups, controlled type 2 DM, if Fasting Blood Glucose (FBG) < 100 mg/ dL and HbA1C < 6.5%, and uncontrolled type 2 diabetes mellitus.

Statistical Analysis:
Univariate and bivariate analysis were performed on research data. The Kolmogorov-Smirnov normality test was used on data with a numerical measuring scale to determine whether the data is normally distributed with a p value> 0.05. Univariate analysis was used for demographic data in order to obtain a characteristic distribution of study participants. Bivariate analysis was used to

determine the mean difference between NLR and LMR values in controlled and uncontrolled type 2 diabetes mellitus groups using an Independent T-test for normally distributed data and Mann Whitney U test for data that were not normally distributed. The test result is significant if the pvalue is <0.05.

Result

The study was carried out on 100 diabetics and 100 subjects were used as controls. The mean age in the diabetics was 51.3 ± 3.6 years and, in controls, it was 61.57 ± 5.73 years. The mean Systolic Blood Pressure (mm of Hg) in the diabetics was 131.5 ± 12.7 and, in controls, it was 115.6 ± 4.98. The mean Diastolic Blood Pressure (mm of Hg) in the diabetics was 90.6 ± 12.6 and, in controls, it was 77.0 ± 4.8.

Table 1: Comparison of Study Parameters Between Cases and Controls

PARAMETERS	CASES	CONTROLS	P-VALUE
AGE	61.57 ± 5.73	51.3 ± 3.6	<0.001
BMI	26.74 ± 3.58	22.7 ± 1.23	<0.001
Systolic Blood Pressure (mm of Hg)	131.5 ± 12.7	115.6 ± 4.98	<0.001
Diastolic Blood Pressure (mm of Hg)	90.6 ± 12.6	77.0 ± 4.8	<0.001

Table 2: Comparison of Blood Investigation between Cases and Controls

PARAMETERS	CASES	CONTROLS	P-VALUE
FBS (mg/dL)	159.53 ± 11.83	86.93 ± 5.39	<0.001
PPBS (mg/dL)	213.1 ± 20.9	130.76 ± 4.51	<0.001
HbA1c	7.69 ± 0.61	4.97 ± 0.25	<0.001
UREA	33.53 ± 3.88	29.4 ± 2.8	<0.001
CREATININE	1.11 ± 0.13	0.78 ± 0.10	<0.001

URIC ACID	6.77 ± 0.52	5.0 ± 0.4	<0.001
Hb	11.25 ± 1.68	11.5 ± 1.5	0.30
WBC	13.06 ± 3.43	14.76 ± 4.47	0.05
NEUTROPHILS	77.46 ± 5.62	75.7 ± 5.6	0.49
LYMPHOCYTES	13.82 ± 4.2	16.4 ± 4.4	0.19
EOSINOPHILS	1.24 ± 1.03	1.12 ± 0.98	0.90
MONOCYTES	6.95 ± 3.48	6.1 ± 2.1	0.76
BASOPHILS	0.47 ± 0.27	032 ± 0.17	0.04
PLATELETS	239.42 ± 69.84	242.7 ± 56.8	0.55

The mean fasting blood glucose in the diabetics was 159.53 ± 11.83 mg/dL and, in controls, it was 86.93 ± 5.39 mg/dL. The mean Postprandial blood glucose in the diabetics was 213.1 ± 20.9 mg/dL and, in controls, it was 130.76 ± 4.51 mg/dL. The mean HbA1c was 7.69 ± 0.61% in the diabetics and 4.97 ± 0.25% in controls. The mean Platelets was 239.42 ± 69.84 in the diabetics and 4.97 ± 0.25% in controls.

Table 3: Comparison of NLR and PLR Between Cases and Controls

PARAMETERS	CASES	CONTROLS	P-VALUE
NLR	6.2 ± 2.1	5.1 ± 2.07	0.03
PLR	18.79 ± 7.81	16.0 ± 6.2	0.193

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 ($p = 0.03$ and $p = 0.193$, respectively) as seen in Table 3.

Discussion

DM is a component of metabolic syndrome that can result in several long-term microvascular and macrovascular complications. [12] 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. [13]

Hyperglycemia increases the release of reactive oxygen species from neutrophils, which, 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. [14]

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. [15] 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. [16] 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. [17]

In our study, 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, respectivel. Diabetic patients had a significantly higher NLR and PLR compared to the controls ($p = 0.03$ and $p = 0.193$, respectively). NLR and PLR increase with increasing severity of glucose intolerance. NLR has been shown to be a better risk factor than total WBC count in the prediction of adverse outcomes. The increased pro-oxidant activity of polymorphonuclear neutrophils has been detected in diabetics, which accelerates the vascular wall degeneration. [18]

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 diabetesassociated complications, which is more precisely done by NLR. [19] Studies by Mertoglu et al. and others showed that higher values of NLR and PLR were associated with increased high insulin resistance. [20] 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. [21]

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. [22]

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. [23] 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. [24]

Conclusion

Neutrophil to lymphocyte ratio (NLR) in the uncontrolled type 2 DM group was significantly higher than in the controlled type 2 DM group. Meanwhile, the lymphocyte to monocyte ratio (LMR) did not significantly differ between the two groups. Further research that did not use secondary data is expected so the patient's body mass index, lipid profile, length of diabetes, and type of therapy can be evaluated.

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