

NEUTROPHIL-LYMPHOCYTE RATIO: A PREDICTOR OF COMPLICATIONS IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract

Background: Chronic inflammation plays a potential role in development of diabetes related complications in type 2 diabetes mellitus (T2DM). Neutrophil-lymphocyte ratio (NLR) is one of the potential markers of systemic inflammation. The objective of this study was to examine an association between NLR and T2DM associated complications.

Methods: A cross sectional study was conducted at Sheikh Zayed Medical College & affiliated hospital in Rahim Yar Khan from June - September 2022. About 360 patients were divided in to three groups. Group A were comprised of T2DM patients without diabetic complications while group B and C were T2DM patients with micro- and macro-vascular complications respectively. Micro- and macrovascular complications were assessed by history, physical examination and medical records. Association of diabetes related complications with NLR value was done using regression analysis with SPSS version 25.

Results: The baseline demographic characteristics of three study groups did not show statistically significant difference. However TLC count is significantly elevated in group B (with microvascular complications) and group C T2DM with macrovascular complications ($P<0.001$) respectively compared to control group A. Similarly NLR ratio was significantly higher (4.8 ± 2.0 & 5.0 ± 1.8) in group B and group C respectively, compared to group A (2.2 ± 0.8 with $P<0.001$). Regression analysis showed that NLR was positively correlated with diabetes related micro and macrovascular complications (OR: 4.62, 95% CI: 2.51-7.26, $p<0.001$) along with HbA1c (OR: 1.732, 95% CI: 1.82-2.22, $P=0.002$).

Conclusion: High NLR ratio is associated with diabetes related micro and macro vascular complications. It should be routinely measured in T2DM patients for prevention of diabetes related complications.

Keywords: NLR, T2DM, Microvascular Complications, Macrovascular complications, Inflammation.

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T2DM is one of the most prevalent form of diabetes which is rising at an alarming rate in both developed and developing countries. Diabetes mellitus

is a multifactorial disease as a number of factors are involved in its pathogenesis. Most T2DM patients remain asymptomatic for a number of years and presents diabetes associated micro and macrovascular complications. This pose an enormous burden both clinically as well as on public health system.¹ Diabetes mellitus is also called the disease of Asians with highest numbers of individuals with this chronic metabolic disorder. It is estimated that number of patients with T2DM almost doubled in South Asian countries over a period of 35 years. There is strong need to take appropriate steps by health authorities to overcome this burden.^{1,2}

The role of inflammation in diabetes associated complications is already well understood. A number

of inflammatory markers have shown positive association with diabetes and its related complications in various clinical studies.^{3,4} However these inflammatory markers cannot be measured in routine clinical practice because of their cost and technical issue in laboratory measurement. Moreover, these inflammatory markers cannot be available in many laboratories in Pakistan as doctors are not favoring these tests too.⁵⁻⁶ NLR is a simple marker of inflammation that can be detected through routine blood complete examination. It is a simple ratio between absolute neutrophil to absolute lymphocyte. NLR is a reliable marker of inflammation and its sensitivity and specificity almost equal to other costly inflammatory markers. Further, it is cheap, easily available and convenient marker of inflammation.⁷⁻¹⁰

Studies have shown strong association with increase NLR value and uncontrolled diabetes. Its high value is not only a predictor of uncontrolled diabetes but also a predictor of cardiovascular disease in type 2 diabetic patients.¹¹⁻¹² NLR value is a predictor of both micro and macrovascular complications in type 2 diabetic patients. Moreover, an increased NLR value is diagnostic and prognostic marker in various cardiovascular and cerebrovascular diseases.¹³

In Pakistan, little work has been done so far to investigate the association of NLR with T2DM and its associated complications. Present study was conducted to see the relationship of NLR value with diabetes related complications.

METHODS

This cross sectional study was conducted at Sheikh Zayed Medical College & hospital Rahim Yar Khan from June 2022 to September 2022. A total of 1050 type 2 diabetic patients were screened at diabetic clinic and outdoor patient department of medical, neurology, nephrology and eye ward on the basis of history, physical examination, fasting blood sugar and HbA1c. Out of 1050, about 360 T2DM patients were enrolled after an informed consent and approval from ethical review board. The criterion was T2DM patients with microvascular (neuropathy, nephropathy, retinopathy) and microvascular (cardiovascular, cerebrovascular)

complications. All these complication were confirmed by history, medical records and physical examination. Patient's medical records include HbA1c, nerve conduction studies, serum urea, serum creatinine, albumin to creatinine ratio, urine complete examination, lipid profile, blood pressure, ECG, carotid Doppler, CT scan, and fundus studies were thoroughly reviewed for inclusion. Patients with history of smoking, alcohol, pregnancy, acute infection, inflammatory conditions, auto-immune diseases, steroids, anti-inflammatory drugs were excluded from the study. A control group without diabetes complications was taken from similar eligible individuals. Patients were divided in to three groups: Group A acted as control and comprised of T2DM patients without complications. Group B comprises of T2DM patients with micro vascular complications while group C served as T2DM patients with macro vascular complications. Five milliliters of overnight blood sample was taken from medial cubital vein. The sample was refrigerated immediately. The sample was sent to the hospital laboratory for total leukocyte count (TLC) count analysis. TLC count including leukocyte, neutrophil, lymphocytes and monocytes values were analyzed by automated chemistry analyzer (micro lab 300). NLR was calculated by dividing the neutrophil to lymphocyte numbers. Data were analyzed by statistical package for social sciences (SPSS-22). Continuous variable were presented as mean±standard deviation while categorical variables presented as percentages. Continuous and categorical variables were assessed by independent sample chi-square test respectively. ANOVA test was used to compare three study groups' parameters. Association of diabetes related complications with NLR value was done with regression analysis. Measure of association was presented as odd ratio 95% confidence interval. A p-value ≤0.005 was considered as statistically significant.

RESULTS

The baseline demographic characteristics of three study groups, i.e. group A (T2DM without complications), group B (T2DM with microvascular complications) and group C (T2DM with macrovascular complications)

are shown in Table 1. Data showed no statistically significant difference in terms of age, sex, diabetes duration, glycemic control, blood pressure and lipid profile. TLC count is significantly elevated in group B (T2DM with microvascular complications) and group C (T2DM with macrovascular complications) with ($P < 0.001$) respectively as compared to control group A (T2DM without complications). Similarly, NLR ratio was significantly higher 4.8 ± 2.0 & 5.0 ± 1.8 in group B and group C respectively as compared to group A with $P < 0.001$. Regression analysis showed that NLR was positively correlated with diabetes related micro and macrovascular complications (OR: 4.62, 95% CI: 2.51-

7.26, $p < 0.001$) along with HbA1c (OR: 1.73, 95% CI: 1.82-2.22, $p = 0.002$). (Table 2).

DISCUSSION

Chronic inflammation plays a potential role in

Table 2: Regression analysis showing odds ratio with 95% confidence intervals as predictor of micro and macrovascular complications in T2DM

	Odds Ratio (OR)	95% confidence interval (CI)	P value
NLR	4.62	2.51-7.26	0.001
TLC	0.876	0.92-1.321	0.56
FBS(mg/dl)	1.012	0.876-1.34	0.42
HbA1c	1.732	1.82-2.22	0.0002
BMI	0.768	0.666-1.841	0.32

Abbreviations: NLR, neutrophil to lymphocyte ratio; FBS, fasting blood sugar, TLC, total leucocyte count, BMI, body mass index

Table 1: Baseline characteristics of study participants ($n = 360$)

Parameters	Group A (N=100) T2DM without complications	Group B (130) T2DM with micro-vascular complications	Group C (N=130) T2DM with macro-vascular complications	P^a
Age (years)	54.8±12.5	62.6±9.5	58.5±10.5	0.45
Male/female ratio (%)	64/36	90/40	85/45	0.82
Duration of diabetes (years)	8.2± 6.2	10.2±5.6	9.4±7.4	0.77
BMI (kg/m ²)	26±3.5	27.5±2.5	28.1±4.2	0.21
Fasting blood sugar (mg/dl)	140±26.5	155±15.2	148±20.5	0.77
HbA1C (%)	6.5± 1.8	8.5±2.5	9.2±3.5	0.002
Systolic blood pressure	130±12.5	142±10.5	135±4.5	0.41
Diastolic blood pressure	90±8.5	92±10.5	85±12.5	0.12
Total Cholesterol	180±36.5	200±20.4	170±15.6	0.22
Triglycerides	150±30.3	142±22.4	155±20.4	0.78
LDL-cholesterol	89±30.2	100±25.5	104±20.4	0.65
HDL-cholesterol	42±8.9	44±9.0	40±7.5	0.44
WBC count × 10 ⁹ /L	7.2±1.8	9.8±4.2	10.5±3.5	0.002
Neutrophil count × 10 ⁹ /L	4.8±3.5	8.2±2.5	8.8±3.2	0.001
Lymphocyte count × 10 ⁹ /L	2.3±0.8	2.4±0.5	2.6±0.7	0.55
NLR	2.2±0.8	4.8±2.0	5.0±1.8	0.001

Abbreviations: BMI, body mass index; NLR, neutrophil to lymphocyte ratio; SD, standard deviation; ANOVA, analysis of variance

Values are mean ± SD or n (%)

^a ANOVA, Chi-square test or Kruskal-Wallis

development of diabetes related complications. NLR is one of the potential markers of systemic inflammation. In present study, we investigated the association of NLR with diabetes related micro and macrovascular complications. We found significant correlation between NLR and diabetes related complications. High value of NLR was observed in T2DM patients with micro and macrovascular complications as compared to T2DM without complications. To our best knowledge very little work has been done so far between NLR and diabetes related complications in Pakistan. NLR is reliable marker of systemic inflammation. NLR can be easily estimated from routine blood complete examination. It is reliable and has a high diagnostic and predictive value to detect atherosclerosis related diseases in T2DM patients. Moreover NLR is also convenient test for poor patients as they cannot afford costly test to detect inflammation such as CRP, IL, TNF, adiponectin and fibrinogen etc.⁷⁻⁹

Various Studies have shown strong association between NLR and T2DM. Highly value of NLR was associated with T2DM, uncontrolled diabetes (i.e increase HbA1C),¹⁴ impaired glucose tolerance.¹⁵ These studies revealed that high NLR value is a predictor of glycemic control in T2DM. People with poor and worst diabetic control have high NLR value as compared to excellent control diabetes. These studies suggested

that NLR could be a vital marker of glucose control in T2DM patients because of its reliability, low cost and easily laboratory monitoring.

A number of studies have shown the association of NLR with T2DM. High NLR value was observed in T2DM patients with insulin resistance.¹⁶ Studies have postulated that high NLR value is a strong predictor of microvascular complications (neuropathy¹⁷, nephropathy¹⁸, retinopathy¹⁹) in T2DM. Similarly studies have shown that high value of NLR is a reliable predictor of macrovascular complications (coronary artery disease, peripheral vascular disease, cerebrovascular disease) in T2DM patients.²⁰

A study found that increase NLR value was strongly associated with diabetes related complications such as cardiovascular disease, cerebrovascular disease, diabetic kidney disease and diabetic retinopathy.²¹ Similarly a study postulated that NLR was associated with coronary microvascular dysfunction in T2DM patients.²² A study observed that increase NLR was significantly associated with diabetic foot complications such as osteomyelitis, increase risk of amputation and septic complications in T2DM patients. A significant relationship was found between NLR and diabetic nephropathy in T2DM patients.²³ The main limitation of our study was the small sample size. Further studies with large sample will be required to clarify NLR association with diabetes related complications. Second limitation of our study was that it is a cross sectional study. NLR is inexpensive, reliable marker of diabetes related complications. NLR should be routinely recommended to T2DM patients in order to identify early complications.

CONCLUSION

High NLR ratio is associated with diabetes related micro and macrovascular complications. It is suggested that NLR should be measured as a routine test in T2DM patients for identifying of diabetes related complications early for prevention.

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