ORIGINAL ARTICLE

Hematological Indices in Controlled and Uncontrolled Type 2 Diabetes Mellitus

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Abstract

Aim and objective: To compare HbA1c levels with inflammatory markers that include a neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) in controlled and uncontrolled diabetics.

Materials and methods: Eighty-nine patients with type 2 diabetes mellitus (T2DM) were divided into two groups of controlled (HbA1c <7%) and uncontrolled (HbA1c >7%) diabetics. Recent laboratory data were used to collect HbA1c (glycated hemoglobin) levels, leukocyte count (WBC), hemoglobin (Hb), hematocrit (Hct), red blood cell distribution width (RDW), neutrophils, lymphocytes, and monocytes. The NLR and MLR were calculated from the laboratory data.

Results: The mean age in controlled and uncontrolled diabetics was 58.30 and 55.62 years, respectively. The mean NLR in controlled and uncontrolled diabetics was 2.61 and 4.88. The difference was found to be statistically significant ($p < 0.05$). The mean MLR in controlled and uncontrolled diabetics was 0.2 and 0.24, but the difference was not statistically significant ($p > 0.05$). A weak positive correlation was found between HbA1c levels and the hematological indices and the results were statistically insignificant.

Conclusion: The study yielded significant results in the difference between controlled and uncontrolled diabetics with respect to NLR. Although there was only a weak positive correlation found between glycated Hb levels and the hematological indices, the results showed that there is a significant difference in the NLR between the two groups. This proves that there is scope for use of these ratios as inflammatory markers in T2DM.

Keywords: Diabetes, Diabetes mellitus, Hematological indices, Inflammation, Inflammatory markers, Microvascular complications, Monocyte-to-lymphocyte ratio, Neutrophil-to-lymphocyte ratio, Type 2 diabetes mellitus.

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Introduction

The global prevalence of diabetes mellitus has been rapidly rising from 4.7% in 1980 to 8.5% in 2014 making it the 6th leading cause of death worldwide.[1] Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by chronic hyperglycemia due to insulin resistance leading to several microvascular and macrovascular complications. Many articles have inferred that an inflammatory response is a likely contributor to insulin resistance and is intensified by chronic hyperglycemia which further aggravates the various complications of diabetes mellitus.[2,3] Diabetes and uncontrolled hyperglycemia are known to play a significant role in the development of cardiovascular disease since the Framingham study. The presence of microvascular complications may lead to coronary events.[4]

In recent years, there has been extensive research on potential systemic inflammatory markers such as neutrophil-to-lymphocyte ratios (NLR) and monocyte-to-lymphocyte ratios (MLR) in various diseases like tumors,[5–8] cardiovascular conditions,[9,10] and other diseases.[11] An increase in these markers are designated as predictors of endothelial dysfunction and inflammation.[12–20]

Over the past 5 years, the NLR has risen to popularity owing to its prognostic value. An increase in NLR is a poor clinical indicator in COVID-19 disease,[21] lung cancer,[22] etc. Endogenous cortisol and catecholamines may be major drivers of the NLR. Increased levels of cortisol are known to increase the neutrophil count while simultaneously decreasing the lymphocyte count.[23] An increase in the MLR is another novel inflammatory marker that could possibly detect vascular disease or complications. Monocytes and monocyte-derived macrophages play important roles in the initiation and progression of atherosclerotic disease.[24–26]

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Diabetes and hyperglycemia create a proinflammatory microenvironment that progresses to microvascular complications, such as, nephropathy, retinopathy, and neuropathy.[27] Obesity is a major risk factor for diabetes and can induce inflammation by toll-like receptor (TLR) activation to recruit proinflammatory cytokines and chemokines.[28] Proinflammatory cytokines, C-reactive protein, tumor necrosis factor (TNF)-α, and interleukin (IL)-6 have all demonstrated increased expression in diabetes.[29] To date, there have been only a few articles that have studied the relationship between diabetes mellitus and these systemic inflammatory markers.[13–17]

We hypothesize that there will be an increase in NLR and MLR while comparing uncontrolled diabetics to controlled diabetics. The goal of our study was to evaluate the differences in NLR and MLR between controlled and uncontrolled T2DM along with correlating HbA1c with NLR and MLR.

Neutrophil-to-lymphocyte ratios and MLR are inexpensive, routinely done, and easily available markers of inflammation. Establishing a concrete association between the hematological indices and HbA1c would help in the utility of these markers in predicting complications of T2DM. Hence, explaining the need for the study.

Materials and Methods

The study protocol was approved by the Institutional Ethics Committee of RajaRajeswari Medical College and Hospital on 21/07/2018. Data were collected from the patients who came to the hospital for follow-up. Forty-three patients served as controlled diabetics (HbA1c <7%), out of which only 39 patients fulfilled the inclusion criteria. Fifty patients served as uncontrolled diabetics (HbA1c >7%). Subjects <25 years and with a history of hepatic failure, acute illness, cancer, and type 1 diabetes mellitus were excluded from the study.

A patient file search was performed to obtain information on HbA1c levels, leukocyte count (WBC), hemoglobin (Hb), hematocrit (Hct), red blood cell distribution width (RDW), neutrophils, lymphocytes, and monocytes. Ratios like NLR and MLR were calculated from the laboratory data.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 22.0 software pack. For data assessment, an independent *t*-test was used for the comparison of hematological indices in controlled diabetics *vs* uncontrolled diabetics. In addition, the Karl Pearson correlation test was performed to compare HbA1c levels with the hematological indices. The *t*-test results were expressed with 95% confidence intervals and a *p* value. The Karl Pearson correlation test results were expressed with an *R* value and a *p* value. A *p* value of <0.05 was considered significant.

Results

A total of 89 diabetic patients were stratified into controlled diabetics (HbA1c <7%, $n = 39$, mean age 58.30 ± 12.02) and uncontrolled diabetics (HbA1c >7%, $n = 50$, mean age 55.62 ± 11.14). The mean Hb, Hct, and RDW levels were comparable between the groups. The mean HbA1c levels were 6.02 ± 0.50% in controlled T2DM and 11.52 ± 2.31% in uncontrolled T2DM. A comparison was drawn between the two groups with respect to demographic and laboratory data using a two-sample *t*-test in Table 1. There were statistically significant differences ($p < 0.05$) between the groups with respect to the following variables, such as, HbA1c levels, WBC count, neutrophil count, and NLR. There were no statistically significant differences found between the groups with respect to the following variables, such as, age, Hb, Hct, RDW, lymphocyte count, monocyte count, and MLR.

Using the Karl Pearson correlation test, a correlation test was done between HbA1c values and the hematological indices which include NLR and MLR in Table 2. It was found that there was a weak positive correlation while comparing HbA1c against NLR and MLR. These results were found to be statistically insignificant.

Table 1: Demographic and laboratory data of controlled and uncontrolled diabetics

Parameters	*HbA1c <7 (controlled) n = 39*	*HbA1c >7 (uncontrolled) n = 50*	*p value*
Age (years)	58.30 ± 12.02	55.62 ± 11.14	0.28
HbA1c (%)	6.02 ± 0.50	11.52 ± 2.31	<0.01*
WBC (10^3/μL)	8.27 ± 2.28	10.34 ± 3.78	0.002*
Hemoglobin (g/dL)	12.72 ± 2.85	12.40 ± 2.43	0.58
Hematocrit (%)	42.04 ± 8.73	40.78 ± 7.36	0.47
RDW (%)	14.76 ± 2.02	13.81 ± 2.46	0.051
Neutrophil (10^3/μL)	5.15 ± 1.85	7.22 ± 4.09	0.002*
Lymphocyte (10^3/μL)	2.22 ± 0.93	2.33 ± 0.88	0.58
Monocyte (10^3/μL)	0.44 ± 0.16	0.48 ± 0.20	0.34
NLR	2.61 ± 1.31	4.11 ± 4.64	0.03*
MLR	0.2 ± 0.08	0.24 ± 0.14	0.27

*p value < 0.05 suggests strong statistical significance using independent *t*-test
NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; RDW, red blood cell distribution width

Table 2: Correlation between HbA1c and hematological indices

HbA1c vs parameters	*R value*	*p value**
HbA1c vs NLR	+0.062	0.55
HbA1c vs MLR	+0.031	0.89

*p value <0.05 suggests strong statistical significance using the Karl Pearson correlation test
NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio

Discussion

The NLR and MLR are relatively newer, simpler, and inexpensive laboratory markers that can be readily estimated. The association between these hematological parameters and many medical pathologies have been clearly established.[18]

The goal of our study was to compare NLR and MLR ratios among controlled and uncontrolled diabetics and then correlate the HbA1c values with these ratios. The mean WBC and neutrophil counts were found to be higher among uncontrolled diabetics with the difference being statistically significant when compared with controlled diabetics.

Higher NLR values (4.11 ± 4.64 vs 2.61 ± 1.31) were found among uncontrolled diabetics when compared with controlled diabetics, respectively. The difference was found to be statistically significant. Higher MLR values (0.24 ± 0.14 vs 0.2 ± 0.08) were found while comparing uncontrolled diabetics (HbA1c >7%) to controlled diabetics (HbA1c <7%), respectively. This difference was found to be statistically insignificant.

A Karl Pearson correlation test was conducted between HbA1c values vs NLR and MLR. There was a weak positive correlation found between the HbA1c levels and the hematological indices. However, the results were statistically insignificant.

Patients with T2DM are at high risk for microvascular complications which is partly due to inflammation. Inflammation is strongly associated with both the secretory function of beta cells and insulin resistance.[12] Circulating inflammatory molecules can decrease beta cell functions directly by secretory dysfunction or

uncontrolled apoptosis.[12] As a result, glucotoxicity and lipotoxicity occur and cause an enhanced inflammatory process.[12] It is well known that inflammation is associated with an increased WBC count. Elevated levels of NLR have been found in diabetes and diabetic nephropathy,[19,20] whereas elevated MLR levels have been found in diabetic retinopathy.[17]

The study conducted by Yue et al. to assess the use of the MLR to predict diabetic retinopathy showed that the MLR was increased in patients with diabetic retinopathy.[17] However, the study did not compare MLR in controlled and uncontrolled T2DM. In our study, the difference in MLR while comparing controlled and uncontrolled T2DM was found to be statistically insignificant. There was a weak positive correlation found between glycated Hb levels and MLR values, but this result was also statistically insignificant.

A study conducted by Demirtas et al. to assess the association of hematological indices with diabetes, impaired glucose regulation, and microvascular complications of diabetes.[12] The study found that there was a statistically significant difference between healthy, control groups, and diabetic groups with respect to NLR. This study shows that there is an increase in inflammatory markers in T2DM. Another study conducted by Hussain et al. on NLR: a good assessment tool of glycemic control in T2DM patients showed that increased NLR values were associated with elevated HbA1c levels and poor glycemic control in patients of T2DM.[28] Although there is only a weak positive correlation present between glycated Hb levels and the ratios, the results of our study showed a significant difference in NLR while comparing controlled and uncontrolled diabetics. Studies comparing HbA1c with inflammatory markers in controlled and uncontrolled diabetics have been promising and this outcome should increase the scope of using these ratios in the evaluation of T2DM.

Our study has some limitations. First, a small sample size from a single institution may not represent the general population. Second, we cannot determine a cause and effect relationship due to the cross-sectional nature of our study.

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