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Evaluation of the Relationship between CRP/Lymphocyte Ratio and Blood Sugar Regulation and Other Metabolic Parameters in Patients with Type 2 Diabetes Mellitus

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Abstract: C-reactive protein to lymphocyte ratio (CLR) has been shown to be associated with diseases characterized by chronic, low-grade inflammation. Since type 2 diabetes (T2DM) is also associated with inflammation, we aimed to study the association between CLR and T2DM. Patients with T2DM who presented to internal medicine outpatient clinics of our institution were divided into 2 groups according to their glycosylated hemoglobin (HbA1c) levels as well-controlled (HbA1c<7%) and poorly controlled (HbA1c≥7%) T2DM groups. Subjects assigned as healthy in routine check-up were included as control group. CLR values of the well and poorly controlled diabetics and control cases were compared. CLR of T2DM group (3.51 (0.03-21.78)) was significantly higher than that of the controls (0.65 (0.02-2.92)) ($p<0.001$). CLR was found to have a sensitivity of 63.2% and a specificity of 97.3% in predicting T2DM. The CLR value of patients with poor diabetic control was 4.76 (0.06-21.78), while the CLR value of patients with well controlled disease was 2.53 (0.03-12.07) ($p<0.001$). The sensitivity and specificity of the CLR in demonstrating poor diabetic control was 41.2% and the 86.1%, respectively. In conclusion, elevated CLR in T2DM patients and even more increased levels in poorly controlled diabetics suggest that CLR could be a useful additional diagnostic tool in treatment follow-up of the T2DM population.

Keywords: type 2 diabetes mellitus (T2DM); c-reactive protein (CRP); CRP/lymphocytes (CLR); inflammation; biomarker

1. Introduction

Type 2 diabetes mellitus (T2DM) affects approximately 537 million adults worldwide [1]. More than 1.5 million deaths each year are directly related to diabetes [2]. Direct healthcare expenditures related to diabetes are already close to one trillion US dollars [3]. T2DM; It is a chronic, metabolic disease characterized by hyperglycemia due to relative impairment in insulin secretion and/or insulin action mechanism (insulin resistance).

Diagnostic criteria are based solely on high glycaemia measurements without providing clear information about the underlying pathophysiology. However, many studies have shown that there is a strong relationship between chronic inflammation and complications of T2DM and T2DM [4-6]. Based on this relationship, many biomarkers; including hematological parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) [7] and C-reactive protein (CRP) [8,9] have been studied to be used in the diagnosis and follow-up of T2DM. In recent years, studies have revealed the role of CRP/lymphocyte ratio (CLR), a new scoring criterion in various chronic and inflammatory diseases such as malignancies, thyroiditis and hepatitis [10-13].

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In present study, we aimed to compare the metabolic parameters and CLR value of the T2DM patients to those in healthy individuals. We further aimed to compare CLR of well controlled diabetic subjects to those with poorly controlled T2DM.

2. Materials and Methods

2.1. Study Design and Setting

After the approval of the institutional ethics committee (approval number: 2022/41, approval date: March 11, 2022), patients diagnosed with type 2 diabetes mellitus who visited the internal medicine outpatient clinics of our institution between March 2022 and August 2022 were included in this retrospective study. T2DM patients included in the study were divided into 2 groups as well-controlled T2DM or poorly controlled T2DM according to their blood glycated hemoglobin (HbA1c) levels (well controlled diabetic subjects with a HbA1c<7% and poorly controlled subjects with a HbA1c≥7%). The control group was healthy volunteers who visited our clinic for routine health control. Subjects with malignancy, acute infection, active inflammatory disease and drug use that may affect lymphocyte count were excluded from the study.

2.2. Clinical and Laboratory Analyses

The age and gender of the participants were recorded. Body mass index (BMI) was calculated with the following formula: weight (kg) / height square (m). CRP, hemogram indices (white blood cell count [WBC], neutrophil count [neu], lymphocyte count [lym], hemoglobin [Hb], Hematocrit [Hct], erythrocyte distribution width [RDW], platelet count [PLT]], mean platelet count volume [MPV], platelet distribution width [PDW]), HbA1c, glucose, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, creatinine, eGFR, urea, 25-OH vitamin D, and The values of spot urine protein and spot urine creatinine analyzes were evaluated. CLR was calculated by dividing CRP by lym. General characteristics, laboratory parameters and CLR levels of well and poorly controlled T2DM and control groups were compared.

2.3. Data Management and Analysis

Statistical analyses were performed with a statistical software (SPSS 20.0 for Windows, IBM Co., Armonk, NY, USA). The Kolmogorov Smirnov test was used to evaluate whether the data were in a normal distribution between the groups. Descriptive statistics for numerical variables were expressed as means (±SD) or medians (minimum-maximum) while categorical variables were expressed as numbers and percentages. In comparison of continuous data, Independent Samples T-test was used in comparison of two independent groups that fit into normal distribution, and the nonparametric Mann Whitney U test was used for data that did not fit into normal distribution. Chi-square test was used to compare categorical data. The correlation between study parameters was analyzed with Pearson's Correlation test. Independent risk factors associated with T2DM and poorly control of the disease were analyzed by Binary Logistic Regression analysis models. ROC analysis was used to determine the cut-off value of CLR for the diagnosis of T2DM and poorly controlled DM. A $p<0.05$ value was accepted for statistical significance level.

3. Results

385 patients were included in the present study. Study groups were determined as 113 healthy controls without any disease and 272 T2DM patients. Then, T2DM patients were divided into 2 groups as well-controlled T2DM and poorly-controlled T2DM. There were 101 patients in the well-controlled T2DM group and 171 in the poorly-controlled T2DM group.

There were 133 (%48.9) men and 139 (%51.1) women in T2DM group while there were 44 (%38.94) men and 69 (%61.06) women in control group. There was no statistically significant difference between the groups in terms of gender distribution ($p=0.074$).

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The mean age was 61.07±9.36 years in the type 2 diabetes mellitus group and 44.91±10.42 years in the healthy control group. Age was found to be statistically significantly higher in patients diagnosed with T2DM (p<0.001).

Table 1. Characteristics of T2DM and control groups.

Group		**Control**		**T2DM**		***p* Value**
Sex		**N**	**%**	**N**	**%**	
	Male	44	38,94	133	48,90	[a]0,074
	Female	69	61,06	139	51,10	
		Median (IQR)				
Age		43 (30-77)		62 (35-89)		[a]**<0,001****
BMI (kg/m²)		26,3 (17,36-44,41)		31(19,59-49,08)		[a]**<0,001****
eGFR (ml/min/1.73m2)		99,02 (65-131)		86,12 (11,77-128,63)		[a]**<0,001****
Urea (mg/dl)		27,4 (12-45)		32 (17-241)		[a]**<0,001****
Creatinine (mg/dl)		0,75 (0,55-1,27)		0,85 (0,39-3,78)		[a]**<0,001****
Spot urine protein/creatinine		193,31 (44,22-273,24)		340,92 (33,3-6873,3)		[a]**<0,001****
Spot urine microalbumin/creatinine		22,61 (1,7-95,43)		44,29 (2,5-4000)		[a]**0,030***
WBC (K/uL)		7,2 (3,21-12,53)		7,48 (3,51-12,5)		[a]**0,091**
LYM (K/uL)		2,23 (1-4,21)		2,21 (0,66-5,08)		[a]**0,757**
HB (g/dl)		13,8 (10,1-16,9)		13,5 (8,1-17,7)		[a]**0,206**
HCT (%)		42,2 (30,1-50,8)		40,76 (25-52)		[a]**<0,001****
PLT (K/uL)		262 (148-463)		266 (112-470)		[a]**0,656**
CLR		0,65 (0,02-2,92)		3,51 (0,03-21,78)		[a]**<0,001****
HbA1c (%)		5,5 (4,1-6)		7,45 (4,9-15,7)		[a]**<0,001****
Glucose (mg/dl)		90 (72-109)		137,5 (71-506)		[a]**<0,001****
CRP (mg/L)		1,4 (0,1-4,7)		8 (0,1-23)		[a]**<0,001****
25-hydroxy vitamin D (µg/L)		13 (3,5-45,3)		15 (3-45,8)		[a]**0,022***
Albumin (g/L)		49 (32-56)		46 (21-56)		[a]**<0,001****

[a] Mann Whitney U Test; * p<0,05; ** p<0,001; BMI, Body Mass Index; CLR, CRP/lymphocyte count ratio; CRP, C-reactive protein; HB, hemoglobin; HCT, hematocrit; HbA1c, glycated haemoglobin; IQR, interquartile range; LYM, lymphocyte count; PLT, platelet count; WBC, white blood cell count.

Median CLR of T2DM and control subjects was 3,51 (0,03-21,78) and 0,65 (0,02-2,92), respectively. Therefore, CLR of the T2DM group was significantly higher than that of the controls (p<0.001).

A positive statistically significant correlation was found between CLR and HbA1c (r=0.410, p<0.001), glucose (r=0.318, p=<0.001), creatinine (r=0.382, p<0.001), spot urine protein/creatinine (r=0.342, p<0.001) and spot urine microalbumin/creatinine ratio (r=0.326, p<0.001).

The area under the curve (AUC) in the ROC curve predicting the presence of T2DM with the CLR was 0.823, which was statistically significant (p<0.001). The CLR value of 2.1998, corresponding

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to the highest Youden index value, was determined as the cut-off value. When we take the CLR cutoff value as 2.1998 and above in estimating the diagnosis of T2DM, the sensitivity was determined as 63.2% and the specificity as 97.3%.

Binary logistic regression analysis adjusted to HbA1c, BMI, eGFR, creatinine, spot urine protein/creatinine and spot urine microalbumin/creatinine ratio showed that CLR was an independent risk factor for T2DM. (p<0.001, OR: 4,012 95%CI 1.912–8.420).

Table 2. Characteristics of well-controlled T2DM and poorly-controlled T2DM group.

Group		**Well-controlled**		**Poorly-controlled**		***p* Value**
Sex		**N**	**%**	**N**	**%**	
	Male	51	50,50	82	47,95	[a]0,685
	Female	50	49,50	89	52,05	
		Mean ± SD		**Mean ± SD**		
Age		59,57±10,23		61,95±8,71		[a]0,043
PLT (K/uL)		271,54±76,39		265,1±72,69		[a]0,489
		Median (IQR)				
BMI (kg/m²)		30,8 (23,31-49,08)		31 (19,59-48,3)		[b]0,542
eGFR (ml/min/1.73m2)		87,06 (44,19-128,63)		84,19 (11,77-119,77)		**[a]0,029***
Urea (mg/dl)		33 (17-86)		32 (17-241)		[a]0,339
Creatinine (mg/dl)		0,83 (0,39-1,23)		0,86 (0,56-3,78)		[a]0,070
Spot urine protein/creatinine		337,82 (40,83-1461,54)		350 (33,3-6873,3)		[a]0,060
Spot urine microalbumin/creatinine		15,63 (2,5-974,14)		30,83 (4,35-4000)		**[a]<0,001****
WBC (K/uL)		7,4 (3,51-12,5)		7,5 (3,63-12,3)		[b]0,590
LYM (K/uL)		2,23 (0,66-5,08)		2,2 (0,66-4,56)		[b]0,714
HB (g/dl)		13,6 (8,2-17,5)		13,4 (8,1-17,7)		[b]0,465
HCT (%)		40,76 (25-51,8)		40,76 (25,3-52)		[b]0,896
CLR		2,53 (0,03-12,07)		4,76 (0,06-21,78)		**[a]<0,001****
HbA1c (%)		6,4 (4,9-7)		8,6 (6,8-15,7)		**[a]<0,001****
Glucose (mg/dl)		112 (71-182)		170 (74-506)		**[a]<0,001****
CRP (mg/L)		4,6 (0,1-22)		12 (0,1-23)		**[a]<0,001****
25-hydroxy vitamin D (µg/L)		15 (5-37)		15 (3-45,8)		**[a]0,029***
Albumin (g/L)		46 (26-53)		46 (21-56)		[a]0,059

[a] Mann Whitney U Test; * p<0,05; ** p<0,001; BMI, Body Mass Index; CLR, CRP/lymphocyte count ratio; CRP, C-reactive protein; HB, hemoglobin; HCT, hematocrit; HbA1c, glycated haemoglobin; IQR, interquartile range; LYM, lymphocyte count; PLT, platelet count; WBC, white blood cell count.

Median CLR of poorly controlled T2DM and well-controlled T2DM patients was 4,76 (0,06-21,78)% and 2,53 (0,03-12,07)%, respectively. Therefore, CLR of the poorly controlled T2DM group was significantly higher than that of the well-controlled T2DM patients (p<0.001).

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The area under the curve (AUC) of the ROC curve predicting poorly controlled T2DM status with the CLR was 0.648, which was statistically significant ($p<0.001$). The CLR value of 6.123, corresponding to the highest Youden index value, was determined as the cut-off value. When we take the CLR cutoff value as 6,123 and above in estimating poorly controlled T2DM, the sensitivity was determined as 41.2% and the specificity as 86.1%.

Binary logistic regression analysis adjusted to timing of the start of T2DM, age, BMI, eGFR, creatinine, spot urine protein/creatinine and spot urine microalbumin/creatinine ratio showed that CLR was an independent risk factor for predicting poorly controlled T2DM. ($p=0.006$, OR: 1,139 95%CI 1.039–1.250).

4. Discussion

The main results drawn from our study are as follows: (a) CLR levels of T2DM patients are significantly higher than the CLR levels of the healthy population, (b) Patients with poorly controlled T2DM have significantly higher CLR levels than patients with well-controlled T2DM, (c) CLR has a considerable sensitivity and specificity for detecting both type 2 DM and poor diabetic regulation, and (d) CLR is an independent risk factor of poorly diabetic control in patients with type 2 DM. Moreover, it was determined that CLR had a positive correlation with HbA1c. CLR was found to have a very high specificity and sufficient sensitivity to predict the presence of T2DM diagnosis. CLR was found to have high specificity and reasonable sensitivity in predicting the presence of poorly controlled T2DM. In addition, the relationship of CLR level with other metabolic parameters was evaluated, and a significant correlation was found between CLR and glucose, creatinine, spot urine protein/creatinine and spot urine microalbumin/creatinine ratio in patients.

The diseases in which CLR, a new biomarker, are most studied seem to be malignancies. Fan et al. showed that CLR is a very strong biomarker reflecting the prognosis of the disease in pancreatic carcinoma and gives more accurate results compared to other biomarkers such as NLR, PLR, CAR, NAR (Neutrophil/Albumin) and PAR (Platelet/Albumin) [14]. He et al. compared CLR with other previously researched scoring parameters (NLR, PLR, CAR, PAR) in predicting prognosis in lung cancers and found CLR superior to them [15]. Apart from these, CLR was found to be significant in demonstrating the prognosis of malignancies in a wide range of studies from gastric cancers [16,17] to oral squamous cell carcinomas [18]. Since malignant diseases are associated with some degree of inflammation as type 2 DM is, elevated CLR levels in patients with type 2 DM in present study is not surprising.

There are many studies in the literature showing the relationship between T2DM and CRP. Liu et al. In the meta-analysis of 19 prospective studies that included 40 thousand participants in total, a significant relationship was found between high CRP and T2DM risk [19]. More recently, Peper et al. According to the results of the REGARDS study, which included more than 30 thousand participants, the risk of T2DM increased significantly when the CRP value was above 3 mg/L [20].

In our study, CLR was shown to be an independent risk factor for T2DM. It has been found that a one-unit increase in CLR level increases the risk of diabetes 4 times. It has been previously reported in other studies that CRP and some other inflammatory markers are similarly independent risk factors for diabetes. Pradhan et al. CRP increases the development of T2DM 15.7 times in a large-scale prospective study. Even when other risk factors were removed, high CRP increased the risk of T2DM development by 4.2 times [8]. CLR is an independent risk factor for poor diabetic control. In this context, it was found that a one-unit increase in CLR level increased the probability of poor diabetic control 1.14 times. Similarly, it has been reported in the literature that inflammatory markers are independent risk factors for diabetic control. Rekeneire et al. In their study, they found the mean CRP values to be 1.17 times higher in patients with high HbA1c and poor glycemic control compared to patients with good glycemic control, and showed that CRP is an independent risk factor in demonstrating poor glycemic control [21].

Because CLR can show the state of inflammation and host immunity as a single marker, it may be a more sensitive prognostic indicator compared to individual parameters (CRP and lymphocyte count). Demirkol et al. showed that CLR was significant in demonstrating liver fibrosis in patients

with chronic hepatitis C [13]. Moreover, in this CLEAR HEP-C study, CLR was reported to have higher sensitivity and specificity rates than all other scores in demonstrating chronic hepatitis C-related inflammation. Again, Demirkol et al. showed that the CLR levels of patients with thyroiditis were significantly higher than the CLR of the healthy population and that CLR could be used as a diagnostic tool [12]. In the CLEAR T study, it was reported that CLR had higher sensitivity and specificity than CRP in demonstrating the inflammatory burden associated with thyroiditis.

Our study has some limitations. First, our study is a retrospective study and due to its cross observational nature, we found only simple association between CLR and type 2 DM rather than causal relationship. Second, our study was conducted in a relatively small cohort. And third, it was conducted in a single center, which prevents globalization of the results. However, to the best of our knowledge, this study is the first study in the literature to examine the relationship between T2DM and CLR, and it is of great clinical importance in terms of determining that CLR is predictive of diabetes and poor diabetic control.

5. Conclusions

The positive correlation of CLR level with HbA1c in patients with type 2 diabetes mellitus and its high sensitivity and specificity in demonstrating the diagnosis of T2DM indicate that CLR can be a reliable and additional diagnostic biomarker. Although not as much as it shows the presence of T2DM compared to the healthy control, its high specificity and reasonable sensitivity in showing the distinction between poorly controlled T2DM and well-controlled T2DM shows that it can be an auxiliary biomarker that can be used in the follow-up of the disease. The significant correlation between CRP-Lymphocyte ratio and serum creatinine, spot urine protein/creatinine and spot urine microalbumin/creatinine ratio shows that it can be used as an additional prognostic biomarker in showing T2DM complications.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Abant Izzet Baysal University (approval number: 2022/41, approval date: 11 March 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data related to this work are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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