Doi: 10.47572/muskutd.1628895

Investigation of the Relationship Between HbA1c Levels and Inflammatory Markers

HbA1c Düzeyleri ile İnflamatuar Belirteçler Arasındaki İlişkinin Araştırılması

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Öz

Çalışmamızın amacı, nötrofil lenfosit oranı (NLR), trombosit lenfosit oranı (PLR), C-reaktif protein (CRP), sedimantasyon ve sistemik immün inflamasyon indeksi (Sİİ) ile HbA1c düzeyleri arasındaki ilişkiyi inceleyerek diyabetli hastalarda olası komplikasyonları ve tedavi sürecini değerlendirmektir. Çalışmaya Ocak 2023 ile Ağustos 2023 tarihleri arasında Aydın Adnan Menderes Üniversitesi Hastanesi'nin ayaktan ve yatan hastalarından HbA1c testleri yaptıranlar dahil edildi. Demografik veriler ve HbA1c, NLR, PLR, SII, sedimantasyon, CRP kaydedildi. Hastalar diyabetsiz (HbA1c<6%), prediyabet (%6-6,4) ve (% ≥6,5) diyabetli olmak üzere 3 gruba ayrıldı. Çeşitli inflamasyon belirteçlerinin düzeyleri farklı hasta grupları arasında karşılaştırıldı. Bulgular: HbA1c düzeyleri ile albumin (p<0,001), CRP (p=0,003), sedimentasyon (p<0,001) ve NLR (p=0,021) arasında istatistiksel olarak anlamlı ilişki saptandı. HbA1c grupları diyabetsiz (<6), prediyabetli (6-6,4) ve diyabetli (>6,5) olmak üzere ayrı kategoriler halinde incelendiğinde diyabetsiz ve prediyabet düzeyinde albumin (p=0,028), CRP (p=0,013) ve sedimentasyon (p=0,014) arasında belirgin bir ilişki gözlendi. Yine diyabetsiz ve diyabetli gruplarda albumin (p<0,0001), CRP (p=0,013), sedimentasyon (p<0,0001) ve NLR (p=0,020) arasında istatistiksel olarak anlamlı bir ilişki saptandı. Prediyabet ve diyabet grupları ile araştırılan inflamatuar belirteçlerden herhangi biri arasında belirgin bir ilişki saptanmamıştır (p>0,05). Çalışmamızın bulguları, diyabetli (>6,5) veya diyabetli olmayan (<6) HbA1c'li hastalarda, NLR ve SII'nin ucuz ve kolay erişilebilir inflamatuar belirteçler olarak kullanılmasının uygulanabilir bir öneri olduğunu göstermektedir.

Anahtar Kelimeler: Diabetes Mellitus, Hba1c, Nötrofil Lenfosit Oranı, Trombosit Lenfosit Oranı

Abstract

The purpose of our study is to evaluate the possible complications and treatment process in diabetic patients by examining the relationship between neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), C-reactive protein (CRP), sedimentation and Systemic Immun Inflamation Index (SII). The study included who had HbA1c tests taken from the outpatient and in hospital patients of Aydin Adnan Menderes University Hospital between January-August 2023. The demographic data and HbA1c, NLR, PLR, SII, sedimentation, CRP were recorded. Patients were divided into 3 groups as non-diabetic (HbA1c<6%), prediabetes (6–6.4%) and (≥6.5%) diabetic. The levels of various inflammation markers were compared between different patient groups. A statistically significant relation was identified between HbA1c levels and albumin (p<0.001), CRP (p=0.003), sedimentation (p<0.001), and NLR (p=0.021). Upon examination of the HbA1c groups as discrete categories, namely non-diabetes (<6), prediabetes (6-6.4) and diabetes (>6.5), at the level of non-diabetes and prediabetes a notable relation was observed between albumin (p=0.028), CRP (p=0.013) and sedimentation (p=0.014). Once more, a statistically significant relationship was identified between albumin (p<0.0001), CRP (p=0.013), sedimentation (p<0.0001) and NLR (p=0.020) in the non-diabetic and diabetic groups. No notable relation was identified between the prediabetes and diabetes groups and any of the inflammatory markers under investigation (p>0.05). The findings of our study indicate that in patients with diabetic (>6.5) or non-diabetic (<6) HbA1c, the use of NLR and SII as inexpensive and readily accessible inflammatory markers is a viable proposition.

Keywords: Diabetes Mellitus, Hba1c, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio

Introduction

Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycaemia and a multitude of complications that affect various organs throughout the body (1). A global estimate suggests that approximately 828 million adults worldwide are affected by diabetes, with a global age-standardized prevalence of approximately 14 percent among adults (2). Type 2 diabetes accounts for approximately 98 percent of global diabetes diagnoses, although this proportion varies significantly among different countries (3). In the United States, the prevalence of diabetes among adults is estimated at 14.7 percent (38.1 million adults), based on data from the National Health and Nutrition Examination Survey (NHANES) from 2017 to 2020. This includes 11.3 percent of individuals (29.4 million adults) with diagnosed diabetes and 3.4 percent (8.7 million adults) with undiagnosed diabetes (4,5). Diabetes remains a significant public health concern in Turkey, with national data indicating that more than seven million adults between the ages of 20 and 79 are affected by the condition. According to the Diabetes Atlas, published by the International Diabetes Federation (IDF), Turkey holds the highest diabetes rate in Europe in terms of age-adjusted comparative diabetes rates. This translates to approximately 15 percent of the population. This data is particularly noteworthy, as it underscores the magnitude of the

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Başvuru Tarihi / Received: 29.01.2025
Kabul Tarihi / Accepted : 07.03.2025

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public health challenge faced by the country (6). In addition to their incidence, diabetes is an important disease that requires early diagnosis and treatment due to its prevalence, its ability to remain asymptomatic for years, and the micro and macrovascular complications it causes. Glycated hemoglobin (HbA1c) is a widely used test for diagnosing diabetes, monitoring treatment response and predicting complications (7). HbA1c is a biomarker that rises in direct proportion to non-enzymatically produced blood glucose concentrations and represents the average blood glucose level over the last two to three months (8,9). Epidemiological studies have shown that DM develops diabetic microvascular and macrovascular complications on the background of a chronic inflammatory process. Neutrophil to lymphocyte ratio (NLR) is considered a major marker of systemic inflammation and is considered an increased risk factor for cardiovascular events. It is a popular and easy test calculated as the ratio of the absolute number of neutrophils and lymphocytes in a complete blood count. It is also thought to be an indicator of subclinical inflammation. NLR, one of the biological reflections of inflammation, is accepted as an indicator of immune response. Increased proinflammatory activity of neutrophils and decrease in lymphocyte levels cause an increase in NLR, which has been associated with the severity of diabetic complications. Many studies have reported that NLR is also associated with increased cardiovascular risk and increased mortality in some cancers. NLR calculation is much cheaper and easier than the measurement of inflammatory markers such as interleukin-6 (IL-6), IL-1 beta, Tumour Necrosis Factor-alpha (TNF-α) (10). Thrombocyte to lymphocyte ratio (PLR) is another test which is determined by the ratio of the number of platelets and lymphocytes in the blood count and has been shown to be associated with the progression of atherosclerosis. It is an indirect indicator of platelet activation and vascular inflammation. The development of atherosclerosis is associated with increased platelet activity and low lymphocyte levels, indicating that PLR is an important marker for predicting diabetic macrovascular complications (11). NLR and PLR are two parameters easily calculated from complete blood count results. Complete blood count is an easy and inexpensive test that can be used in all laboratories. NLR and PLR, which are used as systemic inflammatory markers, are parameters utilised in monitoring the prognosis, mortality and morbidity of many diseases (12). CRP and sedimentation are inflammatory markers frequently used in routine laboratories. Studies have shown that CRP is a more important marker than leucocyte count in insulin resistance. High CRP levels indicate increased insulin resistance and cardiovascular event risk. Many studies have reported that increased CRP levels in diabetic patients are associated with complications such as cardiovascular disease and neuropathy (13). Another inflammatory marker which is currently popular is an innovative marker called Systemic immune-inflammation index (SII). It has a role in predicting the prognosis for tumours and other inflammatory diseases of the organism (14). In the literature, the relationship between SII and many chronic diseases has been analysed. In recent years, SII has emerged as a new biomarker for the assessment of inflammatory response. SII has been found to have significant associations with diabetic nephropathy, ischemic heart disease, and increased epicardial fat tissue (15).

In this study, we aimed to understand the role of inflammatory markers such as NLR, PLR, CRP and SII in the pathophysiology of diabetes by evaluating their relationship with HbA1c levels and to investigate their usability as potential biomarkers in predicting diabetic complications. The evaluation of these markers may contribute to the development of early risk assessment and personalized treatment approaches in diabetes management. From this perspective, we assert that our study constitutes a valuable contribution to the field.

Material and Method

In this study, the data of the patients who admitted to Aydin Adnan Menderes University Hospital outpatients and in hospital patients between January 2023 and August 2023 were obtained retrospectively from the hospital records. Patients whose hemogram, CRP, sedimentation, albumin, and blood gas tests, as well as HbA1c results at the same time included. Hemato-oncology patients using chemotherapy may experience bone marrow suppression, those with systemic infections such as sepsis may have hyperreactive bone marrow, those with chronic and autoimmune inflammatory diseases such as rheumatoid arthritis and those using steroids may have bone marrow suppression, and complete blood count, CRP, albumin, sedimentation, blood gas analyses may be related to the drugs used or the pathogenesis of their diseases. Therefore, patients with these chronic diseases were excluded from the study. Furthermore, patients with incomplete data sets, including those lacking hemogram, CRP, sedimentation, albumin, and blood gas tests, as well as HbA1c results at the same time, were excluded from the study. Demographic data of included patients and HbA1c, NLR, PLR, SII, sedimentation and CRP values were recorded. Patients divided into 3 groups as normal (<6%), prediabetes (6-6.4%) and (5%) diabetes according to the United Kingdom Global Diabetes Association data. Age, gender, additional disease data of these three groups and laboratory test results such as glucose, HbA1c, CRP, sedimentation, complete blood count, SII were retrospectively examined. The objective was to

compare the levels of various inflammatory markers, including NLR, PLR, SII, sedimentation, and CRP, across different patient groups. A cut-off value was calculated for each parameter using the receiver operating characteristic (ROC) analysis. The values found were then compared separately for each group, and their differences and relationships were evaluated.

Power analysis

Power analysis was calculated using G-Power ver. 3.1.9.7 software. In the calculation made with the sample numbers in the groups (Group 1; n=222, Group 2; n=76, Group 3; n=302), the effect size value (f) was determined as 1.89 in NLR, 0.24 in PLR and 0.96 in SII and the real power was calculated as 97.5%, 80.2% and 84.0% for each parameter, respectively. According to Cohen, a scientific study should have at least 80% power and the study was completed with an appropriate power according to this criterion.

Statistical Analysis

The statistical analysis was examined with SPSS statistical package for Windows 26.0 (IBM® SPSS® 26 (SPSS Inc., Chicago, IL, ABD). Descriptive analyses were given as mean±standard deviation, frequency and percentage. Pearson's chi square analysis was used to analyse categorical variables. ANOVA-variance analysis was used for group evaluations. When differences were detected between groups, post hoc Bonferroni test used as pairwise comparison methods. Pearson's chi-square test was used to compare categorical variables. Parameters with predictive properties were determined by ROC analysis. $p<0.05$ considered statistically significant.

Results

A total of 600 patients were included in the study, 52% (n=312) of whom were male and 48% (n=288) female. The mean age of the patients included in the study was 63.12 ±15.99 years. Furthermore, 86% (n=516) of the patients had comorbidities. A total of 52.3% (n=314) of the patients had with diabetes mellitus, while 12.3% (n=74) had chronic kidney disease. Upon examination of the distribution of HbA1c levels among our study, it was observed that 37% (n=222) exhibited levels of <6, 12.7% (n=76) demonstrated levels of 6-6.4, and 50.3% (n=302) displayed levels of >6.5. (shown in Table. 1).

Table 1. Clinical and demographic characteristics of patients

Descriptives	Results	
Age (years) (mean±SD)	63.12±15.99	
Gender n(%)	Male	312 (52)
	Female	288 (48)
Comorbidities n(%)	Yes	516 (86)
	No	84 (14)
Diabetes Mellitus n(%)	Yes	314 (52.3)
	No	286 (47.7)
Chonic Renal Disease n(%)	Yes	74 (12.3)
	No	526 (87.7)
HbA1c n(%)	<6	222 (37)
	6-6.4	76 (12.7)
	>6.5	302 (50.3)

*SD: Standart Deviation

The blood gas, hemogram, serum albumin, CRP, sedimentation, NLR, PLR, and SII values of all patients, in conjunction with HbA1c, are presented in Table 2.

Table 2. Laboratory parameters of the patients

Laboratories	Results
pH (mean ±SD)	7.38±0.07
pCO2 (mmHg) (mean ±SD)	43.28±10.76
HCO3 (mmol/L) (mean ±SD)	25.06±6.09
Lactate (mmol/L) (median (IQR))	1.60 (1.10)
BE (median (IQR))	0.80 (7.38)
Hemoglobine (gr/dL) (mean ±SD)	11.49±2.34
White Blood Cells (10^3/mkrL) (median (IQR))	8945 (5825)
Platelets (10^3/µL) (median (IQR))	261000 (133750)
Neutrophile (10^3/µL) (median (IQR))	6140 (5295)
Lymphocyte (10^3/µL) (median (IQR))	1490 (1125)
Albumine (g/L) (mean ±SD)	35.62±6.70
C-reactive protein (mg/L) (median (IQR))	16.60 (71)
Sedimentation (mm/saat) (median (IQR))	40 (47)
NLR (median (IQR))	4.15 (6)
PLR (median (IQR))	173.28 (160)
SII (median (IQR))	1100.16 (1567.7)

*BE: Base Excess, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index

Table 3 illustrates the albumin, CRP, sedimentation, NLR, PLR and SII values of patients, classified according to their HbA1c levels and the statistical relationships between them. A statistically significant relation was identified between HbA1c levels and albumin ($p<0.001$), CRP ($p=0.003$), sedimentation ($p < 0.001$), and NLR ($p=0.021$). Upon examination of the HbA1c groups as discrete categories, namely non-diabetes (<6), prediabetes (6-6.4) and diabetes (>6.5), at the level of non-diabetes and prediabetes a notable relation was observed between albumin ($p= 0.028$), CRP

Table 3. Statistical relationship between inflammation markers albumin, C-reactive protein, sedimentation, NLR, PLR, SII among 3 groups created according to HbA1c level

Variables	HbA1c level			p	Post hoc p value		
	<6	6-6.4	>6.5		<6 vs	<6 vs >6.5	6-6.4 vs
	(n=222)	(n=76)	(n=302)		6-6.4		>6.5
Albumin	37.6±0.5	35.4±0.7	34.2±0.4	**<0.001**	**0.028**	**<0.0001**	0.546
C-reactive protein	41.2±4.3	71.2±10.0	61.2±4.9	**0.003**	**0.013**	**0.013**	0.964
Sedimentation	34.8±1.8	45.9±3.2	49.3±1.8	**<0.001**	**0.014**	**<0.0001**	1.000
NLR	6.1±0.5	8.2±1.1	8.5±0.6	**0.021**	0.349	**0.020**	1.000
PLR	237.2±23.7	248.4±23.7	237.5±12.1	0.946	1.000	1.000	1.000
SII	1911.4±248.2	1848.2±204.1	2277.3±165.9	0.319	1.000	0.550	0.847

*One-Way ANOVA and post hoc Bonferroni test used. p<0.05 considered significant, *NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index

(p=0.013) and sedimentation (p=0.014). Once more, a statistically significant relationship was identified between albumin (p<0.0001), CRP (p=0.013), sedimentation (p<0.0001) and NLR (p=0.020) in the non-diabetic and diabetic groups. No notable relation was identified between the prediabetes and diabetes groups and any of the inflammatory markers under investigation (p>0.05).

Although there was a notable discrepancy in NLR as a consequence of the comparisons conducted between the groups delineated by HbA1c levels in Table 3, the parameter(s) exhibiting the most robust predictive capacity in each comparison were identified through the comparison of HbA1c levels with one another via ROC analysis (Table 4 and Figure 1).

Table 4. Determination of the predictive properties of NLR, PLR and SII among HbA1c groups

HbA1c Level Groups	Test Result Variables	AUC	Std. Error	p value	95% CI		Sensitivity (%)	Specificity (%)	Cut-off
					Lower Bound	Upper Bound			
6.0-6.4 vs. 6.0	NLR	0.608	0.037	**0.005**	0.535	0.681	60.5	60.4	4.3
	PLR	0.536	0.040	0.350	0.457	0.615	55.3	54.1	173.8
	SII	0.577	0.037	**0.044**	0.504	0.650	60.5	50.5	1063.3
>6.5 vs. <6.0	NLR	0.572	0.025	**0.005**	0.522	0.621	55.0	55.9	3.9
	PLR	0.519	0.025	0.453	0.470	0.569	53.0	52.3	170.9
	SII	0.569	0.025	**0.007**	0.520	0.618	53.0	49.5	1033.2
>6.5 vs. 6.0-6.4	NLR	0.471	0.036	0.438	0.401	0.541	39.7	71.1	3.5
	PLR	0.480	0.037	0.599	0.408	0.553	47.0	55.3	170.9
	SII	0.496	0.035	0.907	0.427	0.564	48.3	60.5	1061.1

*ROC analysis was applied and p<0.05 is significant. *NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index

A comparison of the prediabetes and non-diabetes groups revealed that the NLR and SII parameters exhibited discrimination. A cut-off value of 4.3 was determined for NLR with an AUC of 0.608, sensitivity of 60.5% and specificity of 60.4% (p=0.005). A comparable outcome was observed in the comparison between values diabetes and non-diabetes, with an AUC value of 0.572, a sensitivity of 55.0%, and a specificity of 55.9%, with a cut-off value of 3.9 (p=0.005). In this comparison, the SII parameter also exhibited an AUC value of 0.569, a sensitivity of 53.0%, and a specificity of 49.5% with a cut-off value of 1033.2. No significant predictive feature was identified in the comparison of diabetes and prediabetes groups.

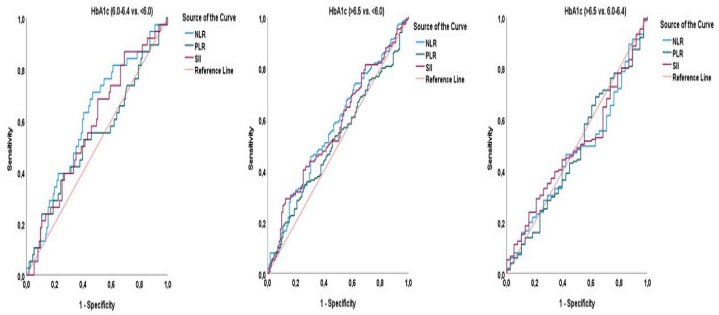

Figure 1. The predictive properties of NLR, PLR and SII among HbA1c groups

Table 5. Comparison of demographic and clinical variables between HbA1c groups

Variables	Subgroups	HbA1c			p value
		<6	6-6.4	>6.5	
Age	N	222	76*	302	***<0.001***
	mean±SD	60.3±17.4	69.6±14.0*	63.6±14.9	
Gender	Male	96(43.2)	38(50.0)	178(58.9)*	***0.002***
	Female	126(56.8)	38(50.0)	124(41.1)	
Chronic disease	No	58(26.1)	6(7.9)	20(6.6)	***<0.001***
	Yes	164(73.9)	70(92.1)	282(93.4)	
Diabetes mellitus	No	166(74.8)	46(60.5)	74(24.5)	***<0.001***
	Yes	56(25.2)	30(39.5)	228(75.5)	
Chronic renal failure	No	200(90.1)	62(81.6)	264(87.4)	0.147
	Yes	22(9.9)	14(18.4)	38(12.6)	
Drug using	No	120(54.1)	26(34.2)	46(15.2)	***<0.001***
	Insulin	10(4.5)	8(10.5)*	34(11.3)*	
	Oral Antidiabetic	62(27.9)	32(42.1)*	138(45.7)*	
	Insulin+OA	30(13.5)	10(13.2)	84(27.8)*	
Presence of Diabetes Complication	No	162(73.0)	46(60.5)	112(37.1)	***<0.001***
	Insulin	60(27.0)	30(39.5)*	190(62.9)*	
Type of complication	No	162(73.0)	46(60.5)	104(34.4)	***<0.001***
	Nephropathy	10(4.5)	4(5.3)	34(11.3)*	
	Retinopathy	4(1.8)	2(2.6)	6(2.0)	
	Cardiopathy	12(5.4)	8(10.5)*	52(17.2)*	
	Diabetic foot	8(3.6)	4(5.3)	28(9.3)*	
	Neurological	10(4.5)	6(7.9)*	24(7.9)*	
	Multiple organ complications	16(7.2)	6(7.9)	54(17.9)*	

*Pearson's Chi Square test used and p<0.05 considered significant, *Indicates significance relative to HbA1c <6.

Demographic and clinical evaluation of patients was performed according to HbA1c values. A subsequent examination of age and gender according to HbA1c values revealed that the mean age of non-diabetic patients (n=222) was 60.3±17.4 years, prediabetic (n=76) 69.6±14.0 years, and diabetic (n=302) 63.6±14.9 years. A statistically significant difference was identified among the age variables when the groups were examined (p<0.001). Furthermore, a statistically significant difference was identified in the mean age of the prediabetic group (p<0.001). A significant difference was found in gender distribution between HbA1c groups (p=0.002). In the diabetic patient group (HbA1c>6.5), the number of male patients (male: 58.9% vs. female: 41.1%) and the presence of chronic disease were found to be significantly higher (p<0.001). There was no significant difference between the HbA1c groups in terms of diabetic chronic renal failure (p=0.147). When drug use (insulin, oral antidiabetic (OA), insulin and OA) was compared, drug use was found to be significantly higher in the diabetic patient group (p<0.001). Diabetic complication development and insulin use were found to be significantly higher in the diabetic patient group among the HbA1c groups (p<0.001). When diabetes complications were examined, nephropathy was found in the diabetic group; cardiopathy was found in the diabetic and prediabetic groups; diabetic foot development and multisystem involvement were found to be significantly higher in the diabetic group (p<0.001), but no significant difference was found in retinopathy (p>0.05). A comparison of these demographic and clinical data is shown in Table 5.

In addition, when HbA1c and inflammation parameters were examined according to gender, a significant difference was found in albumin (p<0.001), CRP (p=0.008), sedimentation (p<0.001), NLR (p=0.027) and SII (p=0.007) parameters among HbA1c groups in male, but no significant difference was found in PLR (p=0.284). In female, a significant difference was found in CRP (p=0.013), NLR (p=0.045) parameters among HbA1c groups, but no significant difference was found in albumin (p=0.100), sedimentation (p=0.736), PLR (p=0.620), SII (p=0.738) parameters.

Discussion

The present study constitutes an original investigation into the relationship between HbA1c levels and inflammatory markers (NLR, PLR, CRP, and SII). A notable strength of our study is its evaluation of the utility of inflammation in predicting the course of diabetes and its potential complications through simple and accessible biomarkers. The incorporation of inflammatory markers derived from widely utilized tests, such as complete blood count, into the clinical decision-making process for diabetic patients is a significant strength of our study, offering substantial practical clinical value.Furthermore, our study was conducted on a substantial patient population, which we believe will make a substantial contribution to the current literature evaluating the prognostic importance of inflammatory markers in individuals with diabetes. A significant strength of our study lies in its exploration of the potential applications of these markers, which are associated with both microvascular and macrovascular complications, in clinical practice. This aspect is particularly noteworthy in terms of the translational value of our study. Furthermore, our detailed examination of the relationship between HbA1c levels and inflammation offers novel insights into the role of chronic inflammation in diabetes management.

The relationship between HbA1c and inflammation can be explained directly and indirectly. Inflammation involves a series of chemical responses triggered by the body's immune system. These responses can increase insulin resistance. Some cytokines released during inflammation, such as TNF-alpha and IL-6, can weaken the effect of insulin. This can lead to increased blood glucose levels. High blood glucose increases the amount of glucose that binds to hemoglobin over time, which increases HbA1c levels. Many studies have observed significant relationships between some inflammatory markers and HbA1c. Therefore, high HbA1c levels can provide information not only about poor blood glucose control but also about a potential inflammatory state. It has been suggested that high HbA1c levels may not only be an indicator of diabetes, but also a sign of inflammation in the body. For all these reasons, it appears that treatments that reduce inflammation (e.g., anti-inflammatory medications, healthy lifestyle changes) may support blood glucose management and lowering HbA1c levels (16). In addition to its role in the primary pathophysiology of diabetes, HbA1c has also been linked to complications such as diabetic nephropathy, neuropathy, and retinopathy that arise due to uncontrolled blood glucose regulation (17). In our study, we examined the relationship between albumin, sedimentation rate and CRP, as well as NLR, PLR and SII, which are traditionally indicators of inflammation, in our patients who were divided into three groups according to their HbA1c levels. This study examines the relationship between both traditional inflammatory markers (albumin, ESR, CRP) and recently prominent immune-inflammatory indices (NLR, PLR, SII) in three different glycemic control groups categorized according to HbA1c levels with a holistic approach for the first time in the literature, and provides an original and comprehensive perspective on the effect of glycemic control on inflammation dynamics in diabetic patients. We believe that it can contribute to the literature in this respect.

In recent years, there has been a preference for the use of NLR and PLR as inflammatory markers in studies conducted on a range of clinical pathologies and patient groups. A 2015 study was conducted in order to investigate the role of the NLR in indicating inflammation in patients with type 2 diabetes mellitus when inflammation due to insulin resistance (IR) is in the subclinical stage. The study examined 413 patients with DM and 130 patients with homeostatic model assessment-insulin resistance (HOMA-IR) >2. A significant relationship was found between increased NLR values and IR (18). In the study conducted by Sefil F et al, glucose regulation in Type 2 DM patients was investigated by grouping HbA1c values as >7% and ≤7% and the relationship between HbA1c values and NLR was examined. In the present study, the fasting serum glucose, neutrophil and WBC counts were found to be significantly higher in group 2 than in group 1. Furthermore, the NLR exhibited a positive correlation with HbA1c. These findings suggest that an elevated NLR may be associated with elevated HbA1c levels in patients diagnosed with type 2 diabetes mellitus. (19). The subjects of study were recruited from Phase 3 of the Chennai Urban Rural Epidemiology Study (CURES). A total of 237 subjects were selected from those with normal glucose tolerance (NGT), 63 from those with impaired glucose tolerance (IGT) and 286 from those with type 2 DM. In this study conducted by Shiny A et al in 2014, individuals with normal and impaired glucose tolerance test results and patients diagnosed with Type 2 DM were selected and NLR values of these 3 groups were compared. The highest NLR values were obtained in Type 2 DM, followed by patients with impaired glucose tolerance. A positive correlation was found between NLR values and HbA1c, fasting plasma glucose and HOMA-IR values (20). There is a paucity of research on the association between the NLR and DM or impaired fasting glucose (IFG). However, a study conducted in 2018 examined the relationship between the fasting plasma glucose (FPG) level and NLR in a Korean population. This cross-sectional retrospective study involved 3219 healthy individuals who attended Konyang University Hospital in South Korea for routine health check-ups

(21). In contrast to the findings of this study, but consistent with those of other studies in the literature, our study demonstrated that NLR was statistically significant with respect to both HbA1c level and comparisons between three HbA1c level groups.

A review of the literature reveals that studies conducted on PLR in diabetes are more limited in number compared to those conducted on NLR. A single-center study published in 2017 regarding PLR from Turkey examined 110 adult patients Mertoğlu et al. conducted a comparative analysis of NLR and PLR values in individuals with normal glucose tolerance, prediabetic patients, individuals with newly diagnosed diabetes undergoing an oral glucose tolerance test (OGTT), and uncomplicated diabetics. It has been observed that NLR significantly decreases in prediabetic and diabetic patients. In the same study, it was found that PLR values decrease in the early stages of prediabetes and diabetes but increase in the advanced stages of diabetes (22). However, in our study, an evaluation of the less studied PLR levels revealed no significant values in any HbA1c level group. This situation demonstrates that diabetes may be associated with the long-term complications of DM, rather than HbA1c levels. As a result, clearer data on PLR can be obtained by conducting randomized controlled studies that include long-term patient follow-up.

C-reactive protein is a sensitive marker of subclinical systemic inflammation associated with hyperglycemia, insulin resistance, and type 2 diabetes mellitus (23). A correlation between plasma CRP concentrations and fasting insulin concentrations has been shown in many studies, indicating that insulin resistance and inflammatory processes are related (24). A prospective, nested case-control study was conducted for the Women's Health Study, an ongoing US primary prevention randomised clinical trial that was initiated in 1992. From a nationwide cohort of 27628 women who were free of diagnosed DM, cardiovascular disease, and cancer at the time of the study's inception, 188 women who subsequently developed diagnosed DM over a 4-year follow-up period were defined as cases. These cases were matched by age and fasting status with 362 disease-free controls. Incidence of confirmed, clinically diagnosed type 2 DM by baseline levels of interleukin-6 (IL-6) and CRP. At the end of study, they reported that the elevated levels of CRP and IL-6 predict the development of type 2 DM. The available data provide support for the hypothesis that inflammation may play a role in the development of diabetes (25). Similarly, our study demonstrated a statistically significant relation with traditional inflammatory markers and HbA1c, including albumin, and CRP. This situation demonstrates the role of inflammation in the physiopathogenesis of patients with uncontrolled glucose monitoring and/or newly diagnosed patients in the development and follow-up of DM.

The innovative marker SII occupies a position in the prediction of the prognosis of the organism in relation to tumours and other inflammatory diseases. A review of the literature reveals that the relationship between SII and numerous chronic diseases has been the subject of examination (14). In a comprehensive study conducted in Turkey, single-center, retrospective, and 3-year patients were examined with a total of 22183 participants and HbA1c and inflammation were examined, and including the control group, prediabetes group, and diabetes group, were divided into three groups according to their HbA1c levels. In the three groups under consideration, the following hemogram-derived new inflammatory markers were evaluated: SII, systemic immune response index (SIRI), and systemic immune aggregate index (SIAI) values, as well as C-reactive protein, sedimentation, and leukocyte values. The results showed that the hemogram-derived inflammatory indices exhibited a gradual increase in patient groups based on HbA1c levels. However, the researchers found weak correlations between HbA1c levels and inflammatory markers as indicators of glucotoxicity (26). In the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2018, this cross-sectional study was conducted among adults suffering from type 2 DM.The objective of this study was to ascertain the potential relationship between SII and diabetic kidney disease (DKD).The study involved 3,937 patients in total, of whom 1,510 (38.4%) had DKD for the diagnosis. Following adjustment for potential confounding variables, multivariable logistic regression revealed that elevated SII levels were associated with an augmented likelihood of DKD. The findings of this study suggest that elevated SII levels are associated with DKD in patients with type 2 DM (27). Song et al. reported a retrospective study on the evaluation of hemogram-derived indices and diabetic patients with peripheral artery disease (PAD). According to their results, SII levels were higher in diabetic patients with PAD compared to those without PAD. They also showed that there was a correlation between the severity of the disease and the indices of inflammation (28). As evidenced by the extant literature investigating the relationship between SII and DM, significant differences were identified between groups in our study when SII levels were examined according to HbA1c levels. This finding serves to reinforce the role of SII in inflammation and demonstrates its association with a biomarker such as HbA1c, which serves as an indicator of glucose regulation.

A substantial body of evidence exists demonstrating the association between diabetes and erythrocyte sedimentation rate, a further non-specific inflammatory marker. Kachekouche et al.

showed in their study that people with high sedimentation rate in the first hour have an 8-fold increased risk of developing type 2 diabetes compared to people with normal sedimentation rate (29). In an investigation conducted by Zhang M. et al. in 2015, the correlation between red cell distribution width (RDW) and microalbuminuria (MAU), and other inflammation markers like a sedimentation rate was examined in a cohort of 320 patients diagnosed with type 2 DM in Zhengzhou. The subjects were stratified into two groups: a normal group and an MAU group. A comparison of the two groups revealed that patients with MAU exhibited higher red blood cell counts and RDW levels compared to those in the normal group. The study also demonstrated that the sedimentation rate is a risk factor for the development of type 2 DM. (30). However, Muscari et al. conducted a study was conducted with the objective of ascertaining the relative relevance of certain inflammatory markers in the context of insulin resistance. Four inflammatory markers (leukocyte count, erythrocyte sedimentation rate, high-sensitivity CRP, and C3 complement) were evaluated as potential determinants of the HOMA index, in conjunction with the five elements of the metabolic syndrome (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III] definition), total cholesterol, physical activity, and four indicators of adiposity (BMI, waist circumference, percent body fat, and hepatic steatosis) in an unselected population of 990 subjects aged 65-91 years (the Pianoro Study). Of the four inflammatory markers that were simultaneously assessed in this elderly population, only C3 was found to be strongly associated with insulin resistance, independently of the components of the metabolic syndrome and the main indexes of abdominal and general obesity but, did not find the relationship between HOMA index and sedimentation significant (31). In our study, a statistically significant relationship was identified between sedimentation rate and HbA1c groups. However, given the existence of contradictory and concordant data in relation to the aforementioned studies, it is evident that further comprehensive research is necessary to elucidate the relationship between sedimentation and inflammation in DM.

A study conducted in our country in 2022 investigated the relationship between the CRP-albumin ratio and HbA1c levels in patients with serum albumin, a negative acute-phase reactant. It is hypothesised that CRP-albumin ratio, a liver-related inflammatory marker, can be employed as an indicator of inflammation in both prediabetes, as defined by HbA1c levels, and patients diagnosed with diabetes mellitus. In this retrospective study, a total of 6993 diabetic patients, 770 patients with prediabetes, and 1340 healthy individuals were included. According to their HbA1c levels, diabetic patients were divided into two groups: controlled diabetes (HbA1c < 6.5%) and uncontrolled diabetes (HbA1c ≥ 6.5%). The study found that the CRP and CRP/Albumin ratio levels were significantly higher in the DM and prediabetes group than in the control group, and that Albumin levels were significantly lower in the DM group than in both the prediabetes and control groups (32). In our retrospective study, the positive acute phase reactant CRP and the negative acute phase reactant albumin were found to have a statistically significant relationship with HbA1c levels, thereby corroborating extant literature data.

A 2021 study conducted in Taiwan, which included 4748 participants between the ages of 30-70, investigated the gender-specific relationship between HbA1c levels and age in Taiwanese adults without diabetes. In this study, it was found that HbA1c levels were positively correlated with age, and that men had significantly higher levels than women. However, no significant positive correlation was found between HbA1c levels and age in men aged 50-70 (33). This shows that HbA1c levels are affected by age and gender, and similarly, in our study, HbA1c levels were found to be significantly higher in men than in women. However, in our study, the mean age of prediabetic patients (HbA1c 6-6.4) was found to be significantly higher than the other groups. This was associated with changes in glycemic indexes related to patients' compliance with diet, medication use and increase in age-related secondary diseases.

In a non-interventional prospective study covering 137 centers in the Czech Republic, patients with diabetic patients whose HbA1c levels could not be controlled with oral antidiabetic drugs and who were treated with a basal insulin regimen were examined for 6 months. A decrease in HbA1c levels was detected with the addition of insulin treatment to oral antidiabetic treatment, but the targeted HbA1c levels were still not achieved (34). Similarly in our study, when the HbA1c values and drug usage of the patients included in our study were examined, HbA1c values were found to be higher in diabetic patients. Those using only insulin or oral antidiabetic drugs were significantly higher in the prediabetic and diabetic groups, while HbA1c levels were found to be significantly higher in patients using insulin and oral antidiabetic combination drugs. Although the treatment of diabetes is carried out in accordance with both diet and drug treatment protocols, there is a need to develop drugs that use new and different pathways to decrease in targeted HbA1c levels.

In a study conducted in Turkey examining 160 adult patients and comparing diabetic complications of patients with HbA1c>12 and HbA1c<7, a significantly higher difference was found in nephropathy, retinopathy, and neuropathy complications in patients with high HbA1c levels.

On the contrary, no significant difference was found in cardiac complications (35). Similarly, in our study, diabetic complications were found to be significantly higher in those with high HbA1c levels and those using insulin. Unlike this study, in our study, nephropathy, cardiopathy, diabetic foot, neurological and multiple organ complications were found to be significantly higher in those with high HbA1c levels, but retinopathy was not found to be significantly higher.

In a retrospective study conducted in Turkey, where non-diabetic, prediabetic and diabetic patient groups were examined, including 124 patients, and there was no gender difference between the groups, the relationship between HbA1c and NLR, PLR, sedimentation and CRP values was investigated. While there was a statistically significant difference in glucose, CRP, sedimentation and neutrophil count values between prediabetic, diabetic and non-diabetic patient groups, no statistically significant difference was found in lymphocyte and platelet count, NLR and TLR values (16). Unlike this study, in our study, there was a significant difference in albumin, CRP, sedimentation, NLR and SII between HbA1c groups in male, but no significant difference was found in PLR. In female, there was a significant difference in CRP and NLR parameters, but no significant difference was found in albumin, sedimentation, PLR and SII parameters. These are different findings supporting that HbA1c is also affected by gender.

A limitation of our single-centre, retrospective study is the lack of long-term follow-up of patients. Nevertheless, we consider this study to be a valuable contribution to the existing literature, given its comprehensive coverage of a large patient population and the inclusion of data from a single centre. To our knowledge, this is the first study to evaluate both traditional inflammation markers such as Albumin, CRP, sedimentation rate and NLR, PLR, SII and also to evaluate HbA1C by separating them into groups. It is imperative that large-scale studies be conducted, taking into account a diverse range of variables, including race, age, gender, treatment duration, and the various subtypes of diabetes (such as Type 1, Type 2, and gestational). Additionally, studies should consider conditions associated with diabetes, such as macrovascular complications. It is therefore evident that further time- and data-based clinical studies are required in order for NLR and PLR values to be incorporated into routine clinical practice.

Conclusion

The results of our study are important elucidating revealing the effect of glycemic control on inflammatory processes in diabetic patients. The increase in inflammatory markers in patients with high HbA1c levels may also provide valuable information in terms of understanding the mechanisms underlying complications such as increased risk of cardiovascular disease in these patients. These findings emphasize that achieving glycemic control in diabetic patients is important not only for blood sugar regulation but also for reducing inflammatory processes and related complications. The results showed that both NLR and SII were significant in diabetic and non-diabetic patient groups as well as in pre-diabetic and non-diabetic patient groups. The findings of our study indicate that using NLR and SII as cheap and easily accessible inflammatory markers in diabetic (>6.5) or non-diabetic (<6) HbA1c patients is a feasible recommendation.

Acknowledgements: None

Conflict of interest statement

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

Ethics Committee Approval: The ethics committee approval for the study was obtained X University Clinical Research Ethics Committee (2023/183).

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

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