

The Relationship Between Hemoglobin A1c and Hemogram-derived Novel Inflammatory Indices

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ABSTRACT

Objective: An increasing number of studies are investigating the importance of new inflammatory markers derived from hemogram in the clinical management of diabetes, which is a chronic inflammatory condition. In this study, we aimed to assess the relation between HbA1c, Systemic Inflammatory Index (SII), Systemic Inflammation Response Index (SIRI), and Systemic Inflammation Aggregate Index (SIAI).

Methods: A total of 22,183 participants, including the control group (n=9100), prediabetes group (n=7087), and diabetes group (n=5996), were divided into 3 groups according to their HbA1c levels. In these 3 groups, hemogram-derived new inflammatory markers SII, SIRI, and SIAI values, as well as C-reactive protein, sedimentation, and leukocyte values, were evaluated.

Results: The median values of all 3 indices were found to be higher in the diabetes group compared to the other groups [SII=515(380-716), SIRI=0.93(0.66-1.35), SIAI=248(164-374), p<0.001]. In the control group, HbA1c and glucose values were not significantly correlated with inflammation indices (p>0.05). However, in the prediabetes group, significant correlations were detected between SII and SIRI values and glucose (r=0.033, p=0.006; r=0.040, p=0.001) and HbA1c levels (r=0.038, p=0.001; r=0.069, p<0.001).

Conclusion: Hemogram-derived inflammatory indices showed a gradual increase in patient groups based on HbA1c levels, but weak correlations were found between HbA1c levels and inflammatory markers as indicators of glucotoxicity. Hemogram is an easily accessible and widely used test in clinical practice. Therefore, hemogram-derived indices may be an alternative to traditional inflammatory markers in assessing glucotoxicity-induced inflammation. The detection of inflammation, which positively correlated with HbA1c levels through new indices, may help in predicting diabetic complications.

INTRODUCTION

Diabetes Mellitus (DM) is seen at a rate of approximately 10% among adults according to the report published in 2021. In the same report, it was stated that the prevalence of DM in Türkiye is 15% and it affects 7 million adults.^[1] In addition to its incidence, diabetes is a disease that requires early diagnosis and treatment due to the microvascular and macrovascular complications it causes. Glycated hemoglobin (HbA1c) is a commonly used test in the diagnosis of diabetes, treatment efficiency, and prediction of complications.^[2] HbA1c is a biomarker that increases in direct proportion to non-enzymatically formed blood glucose concentrations and shows the average blood glucose

level for the last two to three months.^[3] Glucotoxicity caused by chronically high blood glucose levels in patients with elevated HbA1c worsens the prognosis of the disease as it causes inflammation. Glucotoxicity pertains to the damaging effects of high blood sugar levels on tissues and is connected to insulin resistance, which promotes high blood sugar levels. Current studies have shown that chronic hyperglycemia increases the oxidative stress load through the formation of free oxygen radicals, causing inflammation and cell death.^[4,5] Therefore, there are several researches in the literature investigating this dynamic relationship between HbA1c and inflammation.^[6-8] Inflammation can be demonstrated by many biomarkers, as well as by some formulas obtained from a complete blood count,

which is an easily accessible and inexpensive test in clinical practice.^[9] In recent years, systemic inflammatory index (SII), systemic immune response index (SIRI), and systemic immune aggregate index (SIAI) obtained from complete blood count are new inflammatory indices derived from the use of absolute numbers of different cell groups and evaluated in different clinical situations.^[10-12] Studies evaluating new hemogram-derived indices with DM, which is a chronic inflammatory process, are scarcely any. Our study aimed to assess the relationship between HbA1c and SII, SIRI, and SIAI.

MATERIALS AND METHODS

In our study, the data of the patients who applied to the Taksim Education and Research Hospital Internal Medicine outpatient clinic between November 2020 and April 2023 were obtained retrospectively from the hospital records. Ethics committee approval was obtained from Gaziosmanpasa Education and Research Hospital Ethics Committee with the date 07.06.2023 and number 73. All procedures were carried out in accordance with the Helsinki Declaration. Patients aged 18-99 years, hemoglobin levels between 12-16g/dL, and C-reactive protein (CRP) levels <5 mg/dL were included in the study. Patients diagnosed with oncological, rheumatic, and autoimmune diseases, advanced liver and heart failure, pregnancy, and who had type I diabetes mellitus, incomplete information in their medical records were excluded from the study. Participants were divided into three groups according to HbA1c levels. HbA1c values below 5.7% were in the control group, between 5.7-6.4% were in prediabetes, and above 6.5% were in the diabetes group.^[13] HbA1c levels of the patients were measured using ADAMS HV8380V, biochemical tests Roche Cobas c501, complete blood count Mindray BC6800, and erythrocyte sedimentation rate (ESR) Alifax devices.

Formulas of Indices Based on Hemogram:

Systemic inflammatory index (SII) = Neutrophil*Platelet/Lymphocyte,

Systemic inflammation aggregate index (SIAI) = Monocyte*Neutrophil*Platelet/Lymphocyte,

Systemic inflammation response index (SIRI) = Monocyte*Neutrophil/Lymphocyte.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software, version 20.0 was used for the statistical analysis of the study. Normality analyses of the variables were done with the Kolmogorov-Smirnov test. Variables that were not normally distributed were expressed as median interquartile range (25th-75th percentile), while regularly distributed variables were expressed as mean and standard deviation. Categorical variables were expressed as frequency (%). ANOVA for normally distributed parameters and Kruskal-Wallis test for non-normally distributed parameters were used to assess the differences of groups.

The Pearson Chi-square test was performed in terms of categorical parameters. A p-value of <0.05 was considered significant for all analyses.

RESULTS

A total of 22,183 participants, including the control group (n=9100), prediabetes group (n=7087), and diabetes group (n=5996), were categorized into 3 groups according to their HbA1c values. Table 1 summarizes the demographic and laboratory data of the groups. Age distributions were statistically significant in the control, prediabetes, and diabetes groups (41(30-52), 56(47-64), 59(51-67), p<0.001, respectively). 67.6% of participants in the control group, 63.6% in the prediabetes group, and 51.1% in the diabetes group were female, p<0.001. SII, SIRI, and SIAI values, which are inflammatory markers derived from hemogram, were found to be significantly different between the groups. The median values of all 3 indices were found to be higher in the diabetes group compared to other groups [SII=515(380-716), SIRI=0.93(0.66-1.35), SIAI=248(164-374), p<0.001] (Table 1). The correlation of hemogram-derived inflammatory markers with HbA1c and glucose levels is shown in Table 2. While HbA1c and glucose values were not correlated with inflammation indices in the control group (p>0.05), in the prediabetes group, SII and SIRI values were correlated with glucose (r=0.033, p=0.006; r=0.040, p=0.001) and HbA1c levels (r=0.038, p=0.001; r=0.069, p<0.001). Likewise, SIAI values and HbA1c levels (r=0.066, p<0.001) showed a weak positive correlation in prediabetes patients. In the diabetes group, there was a linear relationship between glucose levels, SII, SIRI, and SIAI values (r=0.077, p<0.001; r=0.040, p=0.002; r=0.046, p<0.001, respectively). On the basis of all patients, the highest correlation was found between HbA1c and both SIRI (r=0.112, p<0.001) and SIAI values (r=0.114, p<0.001).

Table 3 summarizes the linear relationship between routine inflammatory markers and HbA1c and glucose levels. In the control group, HbA1c values showed a statistically significant positive correlation with ESR, CRP, and white blood cell (WBC) values (r=0.227, p<0.001; r=0.061, p<0.001; and r=0.046, p<0.001, respectively). In addition, CRP and glucose levels in the control group showed a small correlation but were statistically very significant (r=0.061, p<0.001). In the prediabetes group, correlations were also found between HbA1c levels and inflammatory markers (r=0.135, p<0.001 for CRP, r=0.110, p<0.001 for ESR, and r=0.069, p<0.001 for WBC). Glucose and ESR levels were weakly positively correlated among prediabetes patients (r=0.064, p=0.008). In diabetic patients, glucose and CRP levels were weakly correlated (r=0.079, p<0.001), while HbA1c values were correlated with both CRP (r=0.097, p<0.001) and WBC counts (r=0.070, p<0.001). On the basis of all patients, correlations of glucose values with ESR, CRP, and WBC were found, respectively (r=0.055, p<0.001; r=0.155, p<0.001; and r=0.103, p<0.001). Likewise, linear relationships were observed between HbA1c levels, CRP (r=0.244, p<0.001), ESR (r=0.245, p<0.001),

Table 1. Demographic and laboratory data of the groups

	Control (n=9100)	Prediabetes (n=7087)	Diabetes (n=5996)	p
Age, year	41 (30-52)	56 (47-64)	59 (51-67)	<0.001 *<0.001 **<0.001 ***<0.001
Gender				
Female %	6151 (67.6)	4506 (63.6)	3063 (51.1)	<0.001
Male %	2949 (32.4)	2581 (36.4)	2933 (48.9)	
Glucose, mg/dl	92 (87-98)	101 (93-111)	152 (125-204)	<0.001 *<0.001 **<0.001 ***<0.001
HbA1c, %	5.40 (5.20-5.50)	5.9 (5.8-6.10)	7.70 (6.90-9.20)	<0.001 *<0.001 **<0.001 ***<0.001
Creatinine, mg/dl	0.71 (0.62-0.84)	0.76 (0.65-0.90)	0.80 (0.66-0.96)	<0.001 *<0.001 **<0.001 ***<0.001
AST, U/L	17 (14.06-20.60)	18 (15-21)	17 (14-21.35)	<0.001 *<0.001 **=0.253 ***<0.001
ALT, U/L	15 (11-22)	17 (13-24)	18 (13-26.60)	<0.001 *<0.001 **<0.001 ***<0.001
CRP, mg/dl	1.93 (1.04-3.83)	2.78 (1.43-3.53)	3.74 (1.87-4.07)	<0.001 *<0.001 **<0.001 ***<0.001
ESR mm/h	7 (4-12)	10 (5-18)	11 (6-21)	<0.001 *<0.001 **<0.001 ***=0.021
Hb, g/L	134 (125-145)	133 (124-144)	137 (125-148)	<0.001 *<0.001 **<0.001 ***<0.001
Leukocyte, $\times 10^3/\mu\text{L}$	7.02 (5.95-8.29)	7.38 (6.30-8.69)	7.99 (6.78-9.33)	<0.001 *<0.001 **<0.001 ***<0.001
Neutrophil, $\times 10^3/\mu\text{L}$	4.09 (3.29-5.10)	4.29 (3.48-5.29)	4.78 (3.88-5.82)	<0.001 *<0.001 **<0.001 ***<0.001
Lymphocyte, $\times 10^3/\mu\text{L}$	2.21 (1.84-2.66)	2.33 (1.90-2.84)	2.40 (1.93-2.94)	<0.001 *<0.001 **<0.001 ***<0.001

Monocytes, $\times 10^3/\mu\text{L}$	0.43 (0.35-0.52)	0.45 (0.37-0.55)	0.48 (0.39-0.59)	<0.001 * <0.001 ** <0.001 *** <0.001
Platelets, $\times 10^3/\mu\text{L}$	262 (224-304)	267 (228-311)	265 (222-312)	<0.001 * <0.001 ** =0.039 *** =0.001
SII	479 (357-646)	488 (362-655)	515 (380-716)	<0.001 * =0.003 ** <0.001 *** <0.001
SIRI	0.78 (0.56-1.09)	0.81 (0.59-1.16)	0.93 (0.66-1.35)	<0.001 * <0.001 ** <0.001 *** <0.001
SIAI	203 (138-304)	218 (149-326)	248 (164-374)	<0.001 * <0.001 ** <0.001 *** <0.001

HbA1c: HemoglobinA1c; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; SII: systemic inflammation index; SIRI: systemic inflammation response index; SIAI: Systemic inflammation aggregate index (*: Control vs pre-dm, **: Control vs DM, ***:Pre-dm vs DM).

Table 2. Correlation between hemogram-derived novel inflammatory markers and HbA1c and glucose levels

	SII	SIRI	SIAI
Control			
Glucose	r=0.011 p=0.316	r=0.005 p=0.632	r=-0.011 p=0.285
HbA1c	r=-0.012 p=0.252	r=0.007 p=0.520	r=0.015 p=0.149
Prediabetes			
Glucose	r=0.033 p=0.006	r=0.040 p=0.001	r=0.009 p=0.439
HbA1c	r=0.038 p=0.001	r=0.069 p<0.001	r=0.066 p<0.001
Diabetes			
Glucose	r=0.077 p<0.001	r=0.040 p=0.002	r=0.046 p<0.001
HbA1c	r=0.007 p=0.564	r=-0.014 p=0.283	r=-0.009 p=0.488
All patients			
Glucose	r=0.052 p<0.001	r=0.090 p<0.001	r=0.064 p<0.001
HbA1c	r=0.058 p<0.001	r=0.112 p<0.001	r=0.114 p<0.001

HbA1c: Hemoglobin A1c; SII: systemic inflammation index; SIRI: systemic inflammation response index; SIAI: Systemic inflammation aggregate index.

and WBC ($r=0.180$, $p<0.001$).

As shown in Table 4, according to the regression analysis,

it was seen that uncontrolled diabetes had an effect on hemogram indices.

Table 3. Correlation between routine inflammatory markers and HbA1c and glucose levels

	CRP	ESR	WBC
Control			
Glucose	r=0.061 p<0.001	r=0.026 p=0.232	r=0.018 p=0.078
HbA1c	r=0.137 p<0.001	r=0.227 p<0.001	r=0.046 p<0.001
Prediabetes			
Glucose	r=0.032 p=0.059	r=0.064 p=0.008	r=0.009 p=0.466
HbA1c	r=0.135 p<0.001	r=0.110 p<0.001	r=0.069 p<0.001
Diabetes			
Glucose	r=0.079 p<0.001	r=0.060 p=0.088	r=0.022 p=0.086
HbA1c	r=0.097 p<0.001	r=-0.023 p=0.511	r=0.070 p<0.001
All patients			
Glucose	r=0.155 p<0.001	r=0.055 p<0.001	r=0.103 p<0.001
HbA1c	r=0.244 p<0.001	r=0.245 p<0.001	r=0.180 p<0.001

HbA1c: Hemoglobin A1c; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell.

Table 4. Linear regression analysis for hemogram-derived markers and HbA1c levels

	SII			SIRI			SIAI		
	St.B	95 %CI	p	St.B	95% CI	p	St.B	95 %CI	p
Hba1c	0.053	6.32-12.4	<0.001	0.073	0.021-0.034	<0.001	0.059	5.46-9.90	<0.001
	Adjusted R2=0.003; p<0.001			Adjusted R2=0.005; p<0.001			Adjusted R2=0.003; p<0.001		

SII: systemic inflammation index; SIRI: systemic inflammation response index; SIAI: Systemic inflammation aggregate index St. B: Standardized B value; 95% CI: 95% Confidence interval.

DISCUSSION

We analyzed a total of 22,183 patient records and split them into three study groups: control, prediabetes, and diabetes groups. Female participant percentages were higher in all groups. Our results revealed that hemogram-based inflammatory indices including SII, SIRI, and SIAI gradually increase with glycated hemoglobin levels. In parallel with these results, conventional inflammatory markers such as CRP and ESR were elevated in prediabetic and diabetic patients. Additionally, we assessed the directional relationship between the parameters related to glucotoxicity and inflammatory markers. Glucose and glycated hemoglobin levels were poorly correlated with SII, SIRI, and SIAI levels in both prediabetic and diabetic patients, similarly with CRP, ESR, and WBC levels. However, there was no correlation in diabetic patients. That could be caused by the majority of the diabetic patients having similar HbA1c

levels between 7-8%.

Blood glucose levels are maintained within the physiological range by the balance between tissue glucose consumption, gluconeogenesis, and insulin production. Hyperglycemia results from a disruption in any one of these three mechanisms. It has been shown in various studies that chronic hyperglycemia also causes inflammation through oxidative stress.^[14,15]

Hemogram-derived indices SII, SIRI, and SIAI are markers that are being investigated with increasing interest to determine the systemic inflammation status in various diseases.^[16-19] Liu et al.^[20] assessed the SII levels in type 2 DM patients and showed that SII was an independent risk factor of diabetes mellitus and the patients who had higher SII levels were more likely to develop type 2 diabetes mellitus.

It is known that there is a relationship between HbA1c level and diabetic complications.^[21] The relationship be-

tween hemogram-derived new inflammatory indices and diabetic complications has been shown in various studies. Guo et al.^[22] found a positive correlation between high SII values and the development of diabetic nephropathy in a study of 3937 patients. Song et al.^[23] reported a retrospective study about the assessment of hemogram-derived indices and diabetic patients with peripheral artery disease. According to their results, SII, SIRI, and SIAI levels were higher in the diabetic patients with peripheral artery disease (PAD) compared to the patients without PAD. Also, they showed a correlation between the severity of disease and the inflammatory indices. Similar to previous studies, in our study, SIRI and SIAI, in addition to SII, were found to be higher in the diabetes group than in other groups. In our study, it was observed that CRP, ESR, and WBC levels, which are acute phase reactants commonly used in clinical practice, were positively correlated with HbA1c levels in all three patient groups. In a retrospective study conducted by Demirkol et al.^[24] with 9103 participants, it was shown that CRP values were significantly higher in hyperglycemic conditions. On the other hand, in the study conducted by Elimam et al.,^[25] it was observed that the CRP value was significantly higher in the diabetic group than in the control group, but the same result could not be achieved in terms of ESR. Due to the retrospective design of our study, not being able to access the current treatments and complication status of the patients can be considered as our limitations. We could not obtain HbA1c data simultaneously with repeated hemogram measurements of the same patient in a sufficient number of participants. Therefore, the change in HbA1c was not compared with the change in hemogram-derived indices of the same patient. This can be considered as another limitation of the study.

Conclusion

Hemogram-derived inflammatory indices showed a gradual increase in patient groups based on HbA1c levels, but weak correlations were found between HbA1c levels and inflammatory markers as an indicator of glucotoxicity. Hemogram is an easily accessible and widely used test in clinical practice. Therefore, hemogram-derived indices may be an alternative to traditional inflammatory markers in assessing glycototoxicity-induced inflammation. The detection of inflammation, which positively correlated with HbA1c levels through new indices, may help in predicting diabetic complications. Although new hemogram-derived indices have been studied in various clinical situations, to the best of our knowledge, our study is the first to investigate the relationship of all three indices together with HbA1c levels. Further prospective studies will be required to confirm the results of this study.

Ethics Committee Approval

This study approved by the Gaziosmanpasa Education and Research Hospital Ethics Committee (Date: 07.06.2023, Decision No: 73).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Y., O.E.; Design: S.Y., O.E., A.S., E.B.O.; Supervision: S.Y., A.S., O.E.; Fundings: S.Y., A.S., E.B.O., O.E.; Materials: S.Y., O.E., A.S.; Data: S.Y., O.E., A.S., E.B.O.; Analysis: S.Y., A.S., E.B.O.; Literature search: S.Y., O.E., A.S., E.B.O.; Writing: S.Y., O.E., A.S.; Critical revision: S.Y., O.E.

Conflict of Interest

None declared.

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Hemoglobin A1c ile Hemogram Kaynaklı Yeni İnflamatuvar İndeksler Arasındaki İlişki

Amaç: Kronik inflamatuvar bir durum olan diyabetin klinik yönetiminde hemogramdan elde edilen yeni inflamatuvar belirteçlerin önemini araştıran çalışmaların sayısı giderek artmaktadır. Bu çalışmada HbA1c ile Sistemik inflamatuvar indeks (Sİİ), Sistemik inflamasyon yanıt indeksi (SİYİ) ve Sistemik inflamasyon agregat indeksi (SİAİ) arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Toplam 22183 katılımcı HbA1c düzeylerine göre kontrol grubu (n=9100), prediyabet grubu (n=7087) ve diyabet grubu (n=5996) olmak üzere 3 gruba ayrıldı. Bu 3 grupta hemogramdan elde edilen yeni inflamatuvar belirteçler Sİİ, SİYİ ve SİAİ değerlerinin yanı sıra C reaktif protein, sedimentasyon ve lökosit değerleri değerlendirilmiştir.

Bulgular: Her üç indeksin ortanca değerleri diyabet grubunda diğer gruplara kıyasla daha yüksek bulundu [Sİİ=515 (380-716), SİYİ=0.93 (0.66-1.35), SİAİ=248 (164-374), p<0.001]. Kontrol grubunda, HbA1c ve glukoz değerleri inflamasyon indeksleri ile anlamlı bir korelasyon göstermemiştir (p>0.05). Ancak, prediyabet grubunda Sİİ ve SİYİ değerleri ile glukoz (r=0.033, p=0.006; r=0.040, p=0.001) ve HbA1c düzeyleri (r=0.038, p=0.001; r=0.069, p<0.001) arasında anlamlı korelasyonlar tespit edilmiştir.

Sonuç: Hemogramdan elde edilen inflamatuvar indeksler, HbA1c düzeylerine bağlı olarak hasta gruplarında kademeli bir artış göstermiştir, ancak glukotoksisitenin bir göstergesi olarak HbA1c düzeyleri ile inflamatuvar belirteçler arasında zayıf korelasyonlar bulunmuştur. Hemogram klinik pratikte kolay ulaşılabilen ve yaygın olarak kullanılan bir testtir. Bu nedenle hemogramdan türetilen indeksler, glukotoksisiteye bağlı inflamasyonun değerlendirilmesinde geleneksel inflamatuvar belirteçlere alternatif olabilir. HbA1c düzeyleriyle pozitif korelasyon gösteren inflamasyonun yeni indeksler aracılığıyla saptanması, diyabet komplikasyonlarının öngörülmesinde yardımcı olabilir.

Anahtar Sözcükler: Diabetes mellitus; HbA1c; sistemik immün agregat indeksi; sistemik immün inflamasyon indeksi; sistemik immün yanıt indeksi.