European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024
https://doi.org/10.58600/eurjther2029

Original Research

Systemic Immune Inflammation Index and Neutrophil-to-Lymphocyte Ratio Correlate with Fasting Glucose Levels Among Type 2 Diabetic Patients

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Received: 2024-01-25 **Accepted**: 2024-04-01 **Published Online**: 2024-04-03

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ABSTRACT

Objective: Type 2 diabetes mellitus (T2DM) pathogenesis involves low-grade chronic inflammation, which can be measured via surrogate markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and pan-immune inflammation value (PIIV). They were demonstrated to be correlated with T2DM-related outcomes, including mortality, akin to glycemic indices of fasting blood glucose and glycated hemoglobin. However, it is not clear whether a correlation exists between inflammatory markers and glycemic indices.

Methods: A retrospective study was designed. Clinical and medication variables, glycemic control variables, and complete blood count differential variables were acquired via electronic medical records. NLR, PLR, SIIV, and PIIV values were calculated. Correlation analyses between fasting blood glucose, glycated hemoglobin values, and inflammatory indices were conducted.

Results: Sixty-three patients were included in the study. The median fasting blood glucose and glycated hemoglobin levels were 115 mg/dL and 6.2%, respectively. SII and NLR significantly correlated with fasting blood glucose levels ($r = .271$, $p = .032$, and $r = .364$ $p = .003$, respectively). Although PIIV and NLR showed a correlation trend with glycated hemoglobin ($r = .238$ and $r = .236$, respectively), this correlation did not reach statistical significance ($p = .061$ and $p = .062$, respectively).

Conclusion: This study demonstrated that SII and NLR are not only associated with long-term diabetic complications but are also correlated with the cross-sectional glycemic index of fasting blood glucose. Further studies with larger patient groups have the potential to demonstrate significant correlations between inflammatory indices and glycated hemoglobin levels.

Keywords: Type 2 diabetes mellitus, Glucose, Glycated Hemoglobin, Neutrophil, Lymphocyte

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder with a significant economic and health burden [1]. T2DM-related morbidity is mainly caused by microvascular complications (i.e., neuropathy, retinopathy, and diabetic kidney disease) and macrovascular complications (i.e., atherosclerotic cardiovascular disorders), and various studies indicated that glycemic control is associated with lower T2DM-related complications [2-4]. There is no gold standard methodology to assess glycemic control in T2DM, and new device-based modalities such as continuous glucose monitoring are promising; however, commonly used and widely available methods include

fasting blood glucose (FBG) and glycated hemoglobin [5]. These two methods were consistently shown to be correlated with T2DM-related outcomes, thus forming the main glycemic control targets of treatment protocols [5].

T2DM pathogenesis involves multiple mechanisms, and insulin resistance is the most widely pronounced [6] ; however, emerging data suggests that low-grade chronic inflammation drives both T2DM pathogenesis as well as T2DM-related complications [7, 8]. Since demonstration of tissue-scale inflammatory processes is not straightforward for routine clinical practice, various surrogate markers were developed to reflect multiple aspects of the innate immune system. The most commonly investigated markers are neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and pan-immune inflammation value (PIIV) [9-12]. While the first two markers include the data that their names denote, SII incorporates neutrophils, platelets, and lymphocytes, whereas PIIV comprises monocyte counts in addition to SII. Previous studies indicate a correlation between these inflammatory markers and diabetes-related outcomes as well as cardiovascular and all-cause mortality among diabetic patients [13-14]. However, it is not well defined whether these inflammatory markers are also associated with glycemic control indices such as fasting blood glucose and glycated hemoglobin.

The aim of this study was to investigate the possible relationships between inflammatory markers and glycemic control indices among T2DM patients who receive diabetes treatment.

MATERIALS AND METHODS

This study was designed as a retrospective electronic medical record (EMR)-based study. Patients who were admitted to the general internal medicine outpatient clinic of the Başkent University Ankara Hospital, a tertiary-level academic hospital, between June 1, 2023, and January 1, 2024 were evaluated for eligibility. Patients over 18 years old with a diagnosis of type 2 diabetes mellitus who had clinical and laboratory data in the EMR that were required for the study were included in the study. Demographic and clinical features that are thought to have possible effects on SII, PIIV, NLR, and PLR were acquired via EMR and were as follows: age, gender, and comorbidities of hypertension, rheumatological diseases, pulmonary diseases, and malignancies. Patients who had an acute infection or rheumatological disease flare (both deduced from the clinical notes or laboratory results) were excluded from the study since both could falsely increase the aforementioned indexes and distort the data. Laboratory data that were acquired were fasting levels of blood glucose, glycated hemoglobin, total cholesterol, high and low-density lipoproteins, triglycerides, and counts of leucocytes, neutrophils, lymphocytes, monocytes, and platelets. Four indexes were calculated as follows:

- Systemic immune inflammation index: (neutrophil x platelet) / lymphocyte
- Pan-immune inflammation value: (neutrophil x platelet x monocyte) / lymphocyte
- Neutrophil-to-lymphocyte ratio: neutrophil / lymphocyte
- Platelet-to-lymphocyte ratio: platelet / lymphocyte

Statistical Analysis

Continuous variables were shown as median (interquartile range) or mean (± standard deviation), according to their distribution patterns. Categorical variables were shown as numbers (percentages). Between-group differences for categorical variables were analyzed via Pearson's Chi-squared test ($\chi 2$ test) or Fisher's exact test, if needed. Between-group differences for continuous variables were analyzed using the Student's t-test or Mann–Whitney U test, according to their distribution patterns. Relationships between continuous variables were analyzed using Spearman's correlation test, and Spearman's rho values were provided. All analyses were conducted using IBM SPSS Software version 23.0 (SPSS Inc., Chicago, IL). Two-sided significance testing was performed, and p values less than 0.05 were considered statistically significant.

Main Points:

Type 2 diabetes mellitus (T2DM) pathogenesis involves low-grade chronic inflammation. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and pan-immune inflammation value (PIIV) are inflammatory markers and correlated with T2DM complications but it is not clear whether a correlation exists between inflammatory markers and glycemic indices. This study demonstrated that SII and NLR are correlated with fasting blood glucose in addition to previously demonstrated associations.

RESULTS

Sixty-three patients were found to be eligible to be included in the study, of whom 45 (71.4%) were female, and the median age was 66 (16). All patients except for five were on oral antidiabetic

medications, whereas 18 (28.6%) were on insulin treatment. Statins were used by 25 (39.7%) patients.

Laboratory results demonstrated well-regulated T2DM overall, with a median glycated hemoglobin level of 6.2 (1.4) % and a median glucose level of 115 (36) mg/dL. Regarding complete blood count values, neutrophil, lymphocyte, monocyte, and platelet levels were 4.2 (1.9), 2.4 (0.8), .54 (.17) and 244 (97) x109/L, respectively. The calculated inflammatory index values of NLR, PLR, SII, and PIIV were 404 (310), 231 (184), 1.69 (.83), and 99 (59), respectively. Table 1 demonstrates the demographic, clinical, and laboratory characteristics of patients in detail.

Correlation analysis demonstrated that SII and NLR values correlated with fasting blood glucose levels ($p < .05$). While spearman's rho for the correlation between PIIV and fasting blood glucose was .223, it did not reach statistical significance ($p = .079$), as did PLR. Correlation analysis between glycated hemoglobin and inflammatory indexes was not statistically significant; however, spearman's rho for PIIV and NLR were .238 and .236, respectively, with significance levels of .061 and .062, respectively. Table 2 demonstrates the correlation analysis between fasting blood glucose levels, glycated hemoglobin, and inflammatory indexes. Figure 1 shows the statistically significant correlations with a trendline.

Mann-Whitney-U analysis to analyze whether inflammatory indexes differed with regards to gender, underlying comorbidities, insulin, or statin treatments, but it did not reach statistically significant results (all $p > .05$). However, although the level of significance was .065, NLR levels showed a higher trend in insulin users compared to non-users (1.88 vs. 1.62). Inflammatory indexes did not show a statistically significant correlation with age as well (all $p > .05$).

Table 1. Demographic, clinical and laboratory characteristics of the patients

Feature	Value*
Demographics & Comorbidities	
Age	66 (16)
Gender (Female)	45 (71.4%)
Hypertension	50 (79.4%)
Chronic Kidney Disease	8 (12.7%)
Rheumatological	4 (6.3%)
Pulmonary	6 (8.5%)
Malignancy	4 (6.3%)
Medications	
Oral antidiabetics	58 (92.1%)
Insulin	18 (28.6%)
Statin	25 (39.7%)
Laboratory Values	
Glucose (mg/dL)	115 (36)
Glycated hemoglobin (%)	6.2 (1.4)
Leucocyte ($x10^9$/L)	7.9 (2.5)
Neutrophil ($x10^9$/L)	4.2 (1.9)
Lymphocyte ($x10^9$/L)	2.4 (0.8)
Monocyte ($x10^9$/L)	.54 (.17)
Platelet ($x10^9$/L)	244 (97)
Indexes	
Systemic immune inflammation index	404 (310)
Pan-immune inflammation value	231 (184)
Neutrophil-to-lymphocyte ratio	1.69 (.83)
Platelet-to-lymphocyte ratio	99 (59)

* Numbers in brackets are median levels for continuous variables, and percentages for categorical variables

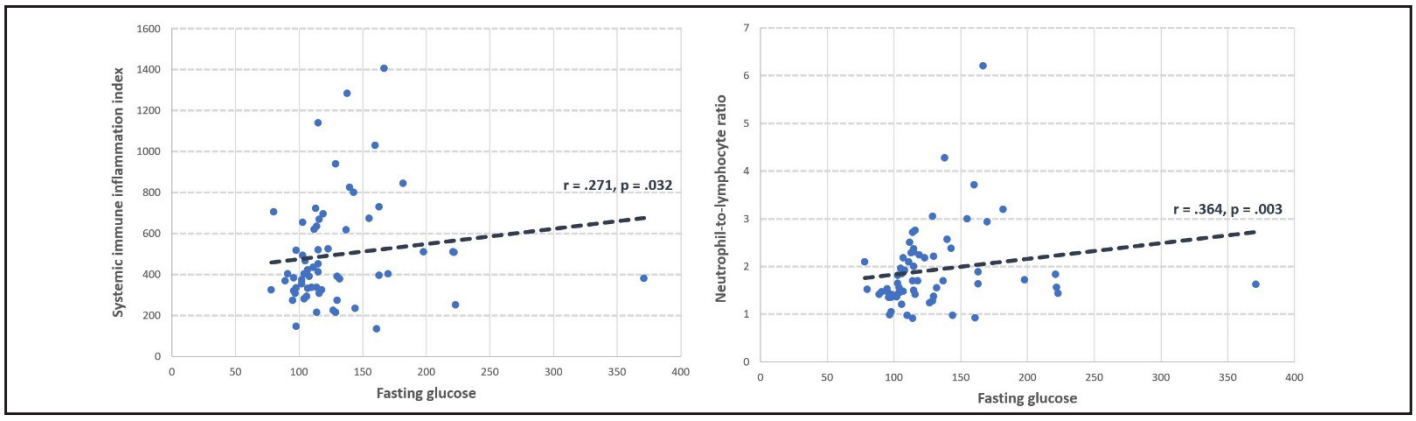

Figure 1. Correlations of systemic immune inflammation index and neutrophil-to-lymphocyte ratio to fasting glucose levels.

Table 2. Correlations between fasting glucose levels and immune indexes, values and ratios

Index	Fasting glucose	Glycated Hemoglobin
Systemic immune inflammation index	**r = .271 , p = .032**	r = .172, p = .177
Pan-immune inflammation value	r = .223, p = .079	r = .238, p = .061
Neutrophil-to-lymphocyte ratio	**r = .364, p = .003**	r = .236, p = .062
Platelet-to-lymphocyte ratio	r = -.019, p = .884	r = -.173, p =.176

Statistically significant correlations are shown in bold

DISCUSSION

This study demonstrated that extensively investigated biomarkers of systemic immune inflammation index and neutrophil-to-lymphocyte ratio values have a positive correlation with fasting blood glucose levels among patients with type 2 diabetes mellitus who receive treatment. This is of particular importance since various studies investigating this relationship have shown associations with long-term outcomes; however, this study described that SII and NLR are correlated with fasting glucose levels even in cross-sectional cohorts.

Various studies have indicated that systemic, low-grade inflammation among T2DM patients is associated with the development of chronic diabetic complications [15]. High-sensitive C-reactive protein (hs-CRP) is an inflammatory marker that is used to define the level of low-grade systemic inflammation. It has been shown that hs-CRP is associated with cardiovascular complications and all-cause mortality [16]. Similarly, the ADVANCE study demonstrated that the pro-inflammatory cytokine interleukin-6 (IL-6) was an independent predictor of macrovascular complications and mortality among diabetic patients [17]. However, both hs-CRP and IL-6 are not widely available, are costly, and are source-consuming; therefore, more feasible approaches are needed to define the level of low-level chronic systemic inflammation. These efforts have led to the emergence of various complete blood count parameter-derived inflammatory markers, of which NLR, PLR, SII, and PIIV are the most extensively studied among both diabetics and non-diabetics. They were first developed for prognosis prediction among malignancies; however, subsequent studies indicated that they are not only associated with outcomes among patients with malignancies but are also associated with outcomes among diabetic patients [13-14].

There are few studies investigating the correlation of inflammatory markers with glycemic indices among diabetic patients. Determination of glycemic control is of paramount importance since treatment intensifications are formed according to fasting blood glucose and glycated hemoglobin levels. Despite their wide use, they have their own limitations; thus, newer methodologies such as continuous blood glucose monitoring systems (CGMS) are being developed to overcome these limitations, but CGMSs have their own constraints as well, such as cost and availability [18]. Considering the limitations of the current glycemic indices and taking into account the disturbances occurring in diabetic patients, pathophysiology-based markers associated with glycemic control are needed. This study has shown that widely available inflammatory markers are associated with fasting blood glucose levels among diabetic patients and have development potential among diabetic patient subgroups, provided that larger patient numbers are involved.

Limitations

This study's limitations are acknowledged. Firstly, this study includes a retrospective cohort, making it prone to biases related to retrospective studies. Secondly, patient number was not high; hence, several correlations could falsely lack significance, such as lack of correlation between PIIV and fasting blood glucose (p = .079), PIIV and glycated hemoglobin (p = .061), as well as NLR and glycated hemoglobin (p = .062). Thirdly, several determinants that could have an effect on the indexes, such as diabetes duration and anti-diabetic medication types, were not evaluated.

CONCLUSIONS

The correlation between fasting blood glucose levels and systemic immune inflammation values, as well as the neutrophil-to-lymphocyte ratio, reflects the low-grade chronic inflammation in type 2 diabetes. Whether these indexes have a role as treatment target markers, such as fasting blood glucose levels or glycated hemoglobin, should be tested in further prospective studies.

Conflict of interest: Author of this manuscript declares no conflict of interest.

Informed Consent: Not applicable.

Funding: No funding was received for this study.

Ethical Approval: This study was approved by the Başkent University Institutional Review Board (Project number: KA24/41).

Author Contributions: Conception: Alper Tuna Güven - Design: Alper Tuna Güven - Supervision: Not applicable - Fundings: Not applicable -Materials: Alper Tuna Güven - Data Collection and/or Processing: Alper Tuna Güven - Analysis and/or Interpretation: Alper Tuna Güven - Literature: Alper Tuna Güven - Review: Alper Tuna Güven - Writing: Alper Tuna Güven - Critical Review: Not applicable.

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How to Cite;

Güven AT (2024) Systemic Immune Inflammation Index and Neutrophil-to-Lymphocyte Ratio Correlate with Fasting Glucose Levels Among Type 2 Diabetic Patients. Eur J Ther. https://doi.org/10.58600/eurjther2029