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Original Article

Impact of SGLT-2 Inhibitors on Aggregate Index of Systemic Inflammation in Patients with Stage 3-4 Chronic Kidney Disease: A Retrospective Cohort Study

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Abstract

Background: Chronic kidney disease (CKD) is characterized by systemic inflammation that contributes to cardiovascular morbidity. The Aggregate Index of Systemic Inflammation (AISI), calculated as (neutrophils × platelets × monocytes)/ lymphocytes, has emerged as a prognostic biomarker. SGLT-2 inhibitors demonstrate anti-inflammatory properties in CKD, yet their impact on AISI remains unexplored. We aim to evaluate the impact of SGLT-2 inhibitor therapy on AISI values in patients with stage 3-4 CKD and type 2 diabetes mellitus.

Methods: This retrospective cohort study included 148 patients with stage 3-4 CKD and type 2 diabetes mellitus who initiated SGLT-2 inhibitor therapy at Gazi University Nephrology Clinic between September 2024 and September 2025. AISI was calculated from complete blood counts at baseline and follow-up (mean 48.0 ± 12.2 days). The primary outcome was change in AISI values. Paired t-test was used for statistical analysis.

Results: Mean age was 67.15 ± 9.20 years, 54.7% were male, and baseline eGFR was 38.9 ± 12.1 mL/min/1.73m². Patients received empagliflozin (n=74) or dapagliflozin (n=74). AISI showed no significant change from baseline to follow-up indicating no significant difference (519.89 ± 319.52 vs. 503.15 ± 442.39, p=0.535).

Conclusions: SGLT-2 inhibitor therapy does not significantly alter AISI values in stage 3-4 CKD patients with diabetes over short-term follow-up. The established cardiovascular and renal benefits of SGLT-2 inhibitors appear to operate through mechanisms not reflected in this composite inflammatory marker.

Keywords: Renal Insufficiency, Chronic, Sodium-Glucose Transporter 2 Inhibitors, Inflammation, Diabetes Mellitus, Type2

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INTRODUCTION

Chronic kidney disease (CKD) represents a major global health burden, affecting approximately 10% of the world's population with particularly high prevalence among patients with diabetes mellitus (1). Beyond progressive decline in kidney function, CKD is characterized by a state of chronic systemic inflammation that contributes substantially to excessive cardiovascular morbidity and mortality observed in this population (2,3). While traditional inflammatory biomarkers such as C-reactive protein (CRP) have demonstrated prognostic value, they capture only limited aspects of the complex inflammatory milieu in CKD (4).

The Aggregate Index of Systemic Inflammation (AISI), calculated as (neutrophils × monocytes × platelets)/ lymphocytes, represents a comprehensive composite biomarker integrating multiple components of the inflammatory cascade (5). By incorporating neutrophils and monocytes, lymphocytes, and platelets, AISI theoretically provides a more comprehensive assessment of systemic inflammatory burden than simpler two-component ratios (6). First introduced in 2018, AISI has demonstrated prognostic value in various conditions including hypertension, heart failure, coronary artery disease, and idiopathic pulmonary fibrosis (7-9).

In CKD populations, AISI demonstrates strong prognostic associations. Analysis of 50,768 participants from the National Health and Nutrition Examination Survey (NHANES) identified a threshold effect at AISI >181.27, above which CKD risk increased sharply (10). Among patients with IgA nephropathy, higher AISI tertiles carried more than double the progression risk compared to lower tertiles (11). Furthermore, in cardiovascular contexts, elevated AISI independently

predicts all-cause and cardiovascular mortality in patients with hypertension, heart failure, and coronary artery disease (7,8,12).

SGLT-2 (Sodium-Glucose Co-Transporter 2) inhibitors have revolutionized CKD management, providing cardiovascular and renal protection across diverse patient populations. The landmark DAPA-CKD, CREDENCE, and EMPA-KIDNEY trials demonstrated consistent 28-44% reductions in kidney disease progression and 29-39% reductions in cardiovascular death or heart failure hospitalization (13-15). These benefits extend to patients with eGFR as low as 20 mL/min/1.73m², establishing SGLT-2 inhibitors as foundational therapy for CKD (16).

SGLT-2 inhibitors exert anti-inflammatory effects through interconnected mechanisms. Metabolic reprogramming increases β-hydroxybutyrate, inhibiting NLRP3 inflammasome activation; concurrent suppression of NF-κB, MKK7/JNK, and JAK2/STAT pathways limits pro-inflammatory gene transcription, while Nrf2/HO-1 activation reduces oxidative stress [17-19]. Clinically, SGLT-2 inhibitors lower IL-6 by 30–65%, TNF-α by ~45%, and CRP by 2–3 mg/L within weeks to months (20,21).

Despite these robust anti-inflammatory effects, the impact of SGLT-2 inhibitors on complete blood count parameters remains unclear. Emerging evidence suggests that while these agents modify cellular function and tissue-level inflammation, they may not significantly alter circulating immune cell populations (22). Since AISI depends on absolute counts of neutrophils, monocytes, platelets, and lymphocytes, it may not capture functional anti-inflammatory changes that occur without quantitative shifts in cell populations (23). This disconnect between functional inflammation and structural hematopoietic parameters represents a fundamental gap in our understanding of SGLT-2 inhibitor mechanisms.

Therefore, this study aimed to evaluate the impact of SGLT-2 inhibitor therapy on AISI values in patients with stage 3-4 CKD and type 2 diabetes mellitus, testing the hypothesis that despite known anti-inflammatory properties, these agents may not significantly alter this composite hematologic marker.

METHODS

Study Design and Participants

This retrospective cohort study was conducted at the Nephrology Clinic of Gazi University Faculty of Medicine, between September 1, 2024, and September 1, 2025. Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Patients were included if they met all of the following criteria:

1.Age ≥18 years
2.Documented stage 3-4 CKD (eGFR 15-59 mL/min/1.73m² calculated using the CKD-EPI equation)
3.Confirmed diagnosis of type 2 diabetes mellitus
4.Initiation of SGLT-2 inhibitor therapy (empagliflozin 10 mg daily or dapagliflozin 10 mg daily) during the study period
5.Available complete blood count data at baseline and follow-up

Patients were excluded if they had any of the following:

1.Active infection at baseline (defined by clinical signs, elevated CRP >10 mg/L, or antibiotic treatment)
2.Recent hospitalization within 3 months prior to baseline
3.Active malignancy or history of malignancy within 5 years
4.Current immunosuppressive therapy (including corticosteroids ≥10 mg/day prednisone equivalent)
5.Discontinuation of SGLT-2 inhibitor before follow-up visit
6.Incomplete laboratory data

Initial screening identified 238 patients with stage 3-4 CKD and type 2 diabetes mellitus who initiated SGLT-2 inhibitor therapy during the study period. After applying exclusion criteria, 148 patients were included in the final analysis (Figure 1). Exclusions comprised: incomplete baseline laboratory data (n=52), lost to follow-up or no control visit (n=48), active infection at baseline (n=24), recent hospitalization within 3 months (n=18), SGLT-2 inhibitor discontinued before follow-up (n=10), active malignancy (n=7), and current immunosuppressive therapy (n=5). Some patients met multiple exclusion criteria.

Data Collection

Demographic and Clinical Data

Baseline demographic data included age, sex, body mass index (BMI), duration of diabetes mellitus, and duration of CKD. Medical history was obtained from electronic medical records, including presence of hypertension, cardiovascular disease, and current medications.

Laboratory Measurements

All laboratory measurements were performed at the Gazi University Hospital Central Laboratory using standardized automated methods. Complete blood counts were obtained using automated hematology analyzers.

Serum creatinine was measured using an enzymatic method, and eGFR was calculated using the 2021 CKD-EPI equation without race adjustment. Glycated hemoglobin (HbA1c) was measured using high-performance liquid chromatography. Serum albumin was measured by bromocresol green method. Urine

albumin-to-creatinine ratio (ACR) was calculated from spot urine samples.

AISI Calculation

AISI was calculated using the following formula:

AISI = (Neutrophils × Monocytes × Platelets) / Lymphocytes

Where all cell counts are expressed as $\times 10^3/\mu L$. AISI was calculated at baseline (before SGLT-2 inhibitor initiation) and at follow-up.

Primary Outcome

The primary outcome was the change in AISI from baseline to follow-up after SGLT-2 inhibitor initiation.

Sample Size Calculation

Sample size calculation was performed using G*Power software (version 3.1). To detect a small-to-moderate effect size (Cohen's d=0.3) in AISI changes with 90% power at a two-tailed significance level of 0.05, a minimum of 119 patients was required. Accounting for an estimated 15% attrition rate, we aimed to enroll at least 140 patients. Our final cohort consisted of 148 patients.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation for normally distributed data. Categorical variables are expressed as frequencies and percentages. Normality of distribution was assessed using the Kolmogorov-Smirnov test. The primary analysis compared baseline and follow-up AISI values using the paired t-test, as data approximated normal distribution.

All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Table 1 presents the baseline characteristics of the 148 patients included in the study. The mean age was 67.15 ± 9.20 years, and 54.7% were male. Mean BMI was 27.3 ± 4.9 kg/m², indicating that most patients were overweight. All patients had type 2 diabetes mellitus with a mean HbA1c of 7.45 ± 0.91% and mean fasting glucose of 130.0 ± 43.6 mg/dL, reflecting generally adequate glycemic control. Baseline mean serum creatinine was 1.82 ± 0.55 mg/dL and mean eGFR of 38.9 ± 12.1 mL/min/1.73m². Serum albumin was at 4.33 ± 0.39 g/dL. Albuminuria was present with mean urine albumin-to-creatinine ratio of 802.5 ± 1118.2 mg/g.

Baseline complete blood count parameters showed mean hemoglobin of 12.5 ± 1.8 g/dL and hematocrit of 38.0 ± 5.5%. Mean white blood cell count was 7.85 ± 2.20 $\times 10^3/\mu L$, with neutrophil percentage of 63.9 ± 9.8% and lymphocyte percentage of 24.1 ± 8.0%. Mean platelet count was 254.9 ± 60.6 $\times 10^3/\mu L$, also within normal limits. Patients received either empagliflozin 10 mg daily (n=74, 50.0%) or dapagliflozin 10 mg daily (n=74, 50.0%). The mean follow-up duration was 48.0 ± 12.2 days.

Primary Outcome: Change in AISI

Table 2 presents the primary outcome results. Baseline AISI was 519.89 ± 319.52, and follow-up AISI was 503.15 ± 442.39. The mean difference was 16.74 ± 327.85 (95% CI: -36.52 to 70.00, p=0.535).

DISCUSSION

This study examined the impact of SGLT-2 inhibitor therapy on the AISI in patients with stage 3-4 CKD and type 2 diabetes mellitus. Our principal finding was that despite initiating SGLT-2 inhibitor therapy, AISI values did not change significantly over a mean follow-up of 48 days. This null result, while perhaps initially counterintuitive given the established anti-inflammatory properties of SGLT-2 inhibitors, provides important mechanistic insights into how these agents exert their cardiovascular and renal protective effects.

Table 1. Baseline Characteristics of Study Population (n=148)

Variable	Mean ± SD or n (%)
Demographics	
Age (years)	67.15 ± 9.20
Male sex	81 (54.7)
Body mass index (kg/m²)	27.3 ± 4.9
Height (cm)	167.3 ± 6.1
Weight (kg)	76.5 ± 14.5
Renal Function	
Serum creatinine (mg/dL)	1.82 ± 0.55
eGFR (mL/min/1.73m²)	38.9 ± 12.1
Serum albumin (g/dL)	4.33 ± 0.39
Urine ACR (mg/g)	802.5 ± 1118.2
Glycemic Control	
Fasting glucose (mg/dL)	130.0 ± 43.6
HbA1c (%)	7.45 ± 0.91
Hematologic Parameters	
Hemoglobin (g/dL)	12.5 ± 1.8
Hematocrit (%)	38.0 ± 5.5
White blood cells ($\times 10^3/\mu L$)	7.85 ± 2.20
Neutrophils (%)	63.9 ± 9.8
Lymphocytes (%)	24.1 ± 8.0
Platelets ($\times 10^3/\mu L$)	254.9 ± 60.6
SGLT-2 Inhibitor	
Empagliflozin 10 mg daily	74 (50.0)
Dapagliflozin 10 mg daily	74 (50.0)

Table 2. Changes in Aggregate Index of Systemic Inflammation Following SGLT-2 Inhibitor Initiation

Variable	Baseline	Follow-up	p-value
AISI	519.89 ± 319.52	503.15 ± 442.39	0.535

AISI, Aggregate Index of Systemic Inflammation

However, the critical finding explaining our results emerges from hematological data: SGLT-2 inhibitors do not significantly alter neutrophil, lymphocyte, monocyte, or platelet counts despite these robust anti-inflammatory effects. This represents a fundamental disconnect between functional cellular changes and circulating cell populations. The EMMY trial post-hoc analysis found no significant changes in neutrophil count, leukocyte count, or neutrophil-lymphocyte ratio with empagliflozin treatment (24). Across all major cardiovascular outcomes trials—EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, CREDENCE, DAPA-CKD, and EMPA-KIDNEY—collectively enrolling over 50,000 participants, no significant platelet count alterations were documented (25).

While SGLT-2 inhibitors modulate lymphocyte function by correcting Th1/Th2 balance and normalizing Th17/Treg ratios, these represent phenotypic and functional changes rather than changes in absolute cell numbers (26). Similarly, functional studies demonstrate that these agents shift monocyte/macrophage polarization from pro-inflammatory M1 toward anti-inflammatory M2 phenotypes and reduce monocyte recruitment from bloodstream to tissues, but circulating monocyte counts remain stable (27). A recent article showed that 15 days of SGLT-2 inhibitor treatment decreased thromboxane B2 by 33.1%, soluble P-selectin by 49.3%, and soluble CD40L by 62.3%, representing potent functional antiplatelet effects without quantitative changes in platelet counts (28).

AISI is calculated as (neutrophils × monocytes × platelets) / lymphocytes, using values (cells $\times 10^3/\mu L$) from routine complete blood counts. Its mathematical structure confers resistance to pathway-specific interventions, as the multiplicative numerator requires concurrent changes in all three cell types for a meaningful effect, while single cell-type targeting has minimal impact. The lymphocyte denominator adds further limitation: although increasing lymphocytes would lower AISI, CKD-related lymphopenia due to thymic involution is largely irreversible with current therapies (29,30).

Biologically, AISI reflects largely irreversible structural immune changes, including thymic involution with reduced naïve T-cell production, myeloid-skewed hematopoiesis due to bone marrow exhaustion, cellular senescence sustaining inflammatory programs, and altered immune trafficking between tissues and circulation (31). These structural alterations are far less modifiable than the functional inflammatory pathways targeted by SGLT-2 inhibitors. Their anti-inflammatory effects arise through reduced cytokine signaling, oxidative stress, endothelial dysfunction, and tissue-level inflammation, without altering circulating immune cell distributions (32).

The one consistent hematological change with SGLT-2 inhibitors involves red blood cells, not AISI components. Hemoglobin and hematocrit increase 2-4 percentage points across all SGLT-2 inhibitor trials through enhanced erythropoiesis mediated by improved renal oxygenation, reversion of myofibroblasts to erythropoietin-producing fibroblasts, and reduced hepcidin levels (33,34).

Our findings have important implications for understanding AISI's clinical utility. AISI serves powerfully as a prognostic marker identifying high-risk CKD patients requiring aggressive management, as demonstrated by studies showing that elevated AISI independently predicts mortality, cardiovascular events, and CKD progression (8-12). However, AISI appears less responsive as a short-term therapeutic marker.

The lack of AISI change despite proven clinical benefit from SGLT-2 inhibitors underscores the importance of selecting inflammatory markers aligned with therapeutic mechanisms. IL-6, CRP, and oxidative stress markers more accurately reflect SGLT-2 inhibitor–mediated anti-inflammatory activity than AISI. More broadly, anti-inflammatory strategies targeting cellular function, activation states, or signaling pathways may yield substantial clinical benefit without altering composite indices dependent on structural hematopoietic changes. In contrast, CRP, IL-6, TNF-α, and to a variable extent NLR respond to pharmacologic interventions, as they represent soluble or dynamic inflammatory components. AISI, however, requires shifts in circulating cell populations, a threshold largely resistant to current anti-inflammatory therapies.

In CKD populations, studies noted AISI was more effective in detecting CKD presence than simpler inflammatory markers like SII or PLR, suggesting it captures a different aspect of disease burden—likely reflecting chronic structural immune remodeling rather than acute or subacute inflammatory states (10). This distinction becomes crucial when interpreting therapeutic interventions.

The major CKD trials proved SGLT-2 inhibitors reduce hard outcomes by 28-44% for kidney disease progression and 29-39% for cardiovascular death or heart failure

hospitalization without measuring inflammatory biomarkers, demonstrating that mechanistic understanding, while valuable, is not required for evidence-based prescribing (13,14). Our null finding should not deter clinicians from prescribing SGLT-2 inhibitors in appropriate patients, as these agents provide cardiovascular and renal protection through mechanisms that extend beyond what AISI captures.

This study has several strengths. We utilized a well-defined cohort of patients with documented stage 3-4 CKD and type 2 diabetes mellitus, a population known to benefit from SGLT-2 inhibitor therapy. We employed rigorous inclusion and exclusion criteria to minimize confounding from acute inflammatory conditions. Our sample size exceeded the calculated requirement based on power analysis. We calculated AISI using standardized automated laboratory methods, enhancing reproducibility.

However, several limitations merit discussion. The retrospective design introduces potential selection bias, though consecutive enrollment of eligible patients mitigated this risk. The relatively short follow-up duration (mean 48 days) may not capture longer-term inflammatory changes, though previous studies demonstrating

SGLT-2 inhibitor anti-inflammatory effects typically observed changes within 30-90 days (20,21). The single-center design limits generalizability, though our patient population is representative of typical CKD patients seen in nephrology clinics.

We did not measure other inflammatory markers (IL-6, TNF-α, CRP) that might have changed despite stable AISI, preventing direct demonstration of anti-inflammatory effects in our cohort. We captured only single baseline and follow-up measurements rather than serial assessments, potentially missing temporal variability.

The relatively short follow-up precluded assessment of clinical outcomes such as CKD progression or cardiovascular events. Future studies with longer follow-up examining both AISI changes and clinical outcomes would clarify whether AISI dynamics predict response to SGLT-2 inhibitor therapy. Additionally, we did not assess changes in individual complete blood count components, which might have revealed subtle shifts not reflected in the composite AISI calculation.

Mechanistic studies should determine which aspects of systemic inflammation drive AISI's prognostic value whether specific cell types contribute disproportionately and whether targeted hematopoietic interventions could modify AISI. Comparative studies examining AISI versus simpler markers (NLR, PLR) across CKD stages and etiologies would optimize risk stratification approaches. Investigation of interventions that might alter hematopoietic parameters such as senolytic therapies targeting senescent cells or interventions addressing thymic involution could clarify whether structural immune aging represents a modifiable therapeutic target.

CONCLUSION

Our findings indicate that cardiovascular and renal benefits of SGLT-2 inhibitors arise from mechanisms not captured by this composite hematologic marker. Inflammation spans circulating cytokines, cellular activation, and structural immune remodeling, with therapies targeting distinct components. AISI reflects structural immune changes resistant to current anti-inflammatory strategies, whereas SGLT-2 inhibitors modulate functional pathways without altering cell counts.

Clinicians should not expect AISI reductions after SGLT-2 inhibitor initiation despite established anti-inflammatory effects. Stable AISI values alongside improved markers reflect insensitivity rather than treatment failure. Decisions should prioritize eGFR preservation, proteinuria reduction, and cardiovascular event prevention over biomarker fluctuations in practice.

DECLARATIONS

Ethics Committee Approval: TThis study was approved by the Gazi University Ethics Committee (approval number: 2025-1097, approval date: June 17, 2025). The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study using de-identified data from medical records, the requirement for informed consent was waived by the ethics committee.

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: The authors declare no competing interests.

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Authors' Contributions

BCH: Conceptualization, methodology, data curation, formal analysis, writing—original draft, writing—review and editing. TEC: Data collection, validation, writing—review and editing. AK: Data collection, validation, writing—review and editing, HP: Conceptualization, writing—review and editing. All authors read and approved the final manuscript.

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