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The Impact of Empagliflozin on Inflammatory Markers in Adults with Type 2 Diabetes: A Retrospective Cohort

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Abstract

Background: Inflammation plays a significant role in the development and progression of type 2 diabetes (T2D). Empagliflozin, an SGLT2 inhibitor, has shown some anti-inflammatory effects in patients with T2D. This study aimed to evaluate the impact of empagliflozin on some inflammatory markers in T2D.

Methods: This retrospective single-arm cohort study included 40 patients with T2D who were treated with empagliflozin. Inflammatory markers such as serum level of erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hs-CRP), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and serum albumin were evaluated at baseline and 12 weeks after empagliflozin treatment. Statistical analysis used paired samples t test, and the statistically significant level was considered $P < 0.05$.

Results: After 12 weeks, a significant reduction was found in ESR (17.75 ± 15.7 mm/hr to 14.72 ± 10.93 mm/hr; $P = 0.025$). However, the decrease in hs-CRP did not reach significance ($P = 0.936$). NLR did not show a significant reduction ($P = 0.962$), but there was a trend toward a significant decrease in PLR (107 ± 33 to 100 ± 35; $P = 0.053$). The neutrophil count did not change significantly ($P = 0.247$), but the lymphocyte count significantly increased (2.43 ± 7.85 to 2.57 ± 7.45 109/l; $P = 0.014$). Serum albumin showed a significant increase (42.8 ± 3.4 to 45.6 ± 3.2 g/l; $P < 0.001$), indicating a decrease in inflammation.

Conclusion: Empagliflozin showed anti-inflammatory effects by reducing ESR and PLR and increasing serum albumin and lymphocyte count in adults with T2D. Monitoring inflammatory markers can serve as an indicator of treatment effectiveness in T2D patients.

Keywords: Empagliflozin, Type 2 diabetes, Inflammatory

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Introduction

Diabetes is predicted to affect 578 million people worldwide by 2030 and roughly 700 million by 2045. Inflammation plays a significant role in the pathogenesis of type 2 diabetes (T2D), contributing to the development of T2D and its associated complications. Furthermore, there is a strong correlation between inflammation and poor glycemic control. Recently, there has been a growing interest in targeting inflammatory pathways to prevent and manage T2D. Furthermore, it is believed that this strategy may also positively impact reducing the complications associated

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↑What is "already known" in this topic:
In the pathogenesis of T2D, inflammation plays a significant role. The main cause of mortality in patients with T2D is atherosclerotic cardiovascular disease, which can be promoted by inflammation. Empagliflozin has garnered attention for its potential anti-inflammatory effects.

→What this article adds:
Based on our findings, empagliflozin can reduce ESR and PLR while increasing serum albumin and lymphocyte count in T2D, which can suggest the anti-inflammatory effect of empagliflozin.

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with diabetes. One of the most common complications of diabetes is cardiovascular disease, which can result in mortality in these patients (1-4).

Different drug classes are available for managing diabetes. One notable development in the field is the widespread use of SGLT2 inhibitors for cardiovascular benefits. Among these inhibitors, empagliflozin has garnered attention for its potential anti-inflammatory effects. Studies conducted a few years ago have shown that empagliflozin can reduce rodent inflammatory markers, further highlighting its potential therapeutic value (5). Additionally, there is some evidence indicating the anti-inflammatory properties of this medication. Lannantuoni et al conducted a study that revealed that empagliflozin decreases the level of highly sensitive-C-reactive protein (hs-CRP). These findings highlight the potential anti-inflammatory effects of the drug (6). Moreover, another study by Doğan et al proposed using neutrophil/lymphocyte ratio (NLR) as a practical marker of inflammation in patients with T2D. This suggests that NLR could be a useful indicator for assessing inflammation in T2D (7).

However, in a recent investigation, no significant differences were observed in the decline of hs-CRP, neutrophil count, leukocyte count, NLR, and platelet to lymphocyte ratio (PLR) between the placebo group and the empagliflozin group in the setting of acute myocardial infarction (8). Mohaghegh et al showed no significant reduction in hs-CRP with empagliflozin (9). Furthermore, there was a restricted amount of data about the impact of empagliflozin on the serum concentration of albumin as a negative inflammatory marker (2).

Because T2D has an inflammatory feature, which led to the conduct of this study, its management can help avoid or control diabetes and its complications.

The leading cause of mortality in patients with T2D is atherosclerotic cardiovascular disease, which can be promoted by inflammation (1-4). Thus, cardiovascular events can be managed or prevented by controlling the inflammation in these patients. Thus, this study aimed to evaluate the effect of empagliflozin as an SGLT2 inhibitor on some inflammatory markers in these patients.

Methods

Study Design and Setting

This retrospective, single-arm cohort study aimed to investigate the effect of empagliflozin on inflammatory markers in patients with T2D. The study was conducted at Hazrat Rasool Hospital in Tehran between January and February 2023.

Participants

In this study, data recording of patients with T2D who were treated with empagliflozin 10 mg once daily were evaluated, and patients who met the inclusion criteria—including patients with T2D, aged 18 to 80 years, known time of starting empagliflozin and persistence of consumption for at least 12 weeks, and estimated glomerular filtration rate (GFR) of >60 mL/min/1.73 m^2—were assessed. The exclusion criteria were a history of rheumatologic or any chronic inflammatory diseases, active infectious diseases, and a history of corticosteroid intake that was recorded in their datasheet.

Variables

The primary outcomes of this study were some available inflammatory markers, including hsCRP, erythrocyte sedimentation rate (ESR), leukocyte count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and serum albumin. The same variables were evaluated after 12 weeks of empagliflozin treatment. The potential confounders were chronic inflammatory diseases, active infectious diseases, and a history of corticosteroid intake all of them were considered in the exclusion criteria. Indeed, we only included patients with GFR of >60 mL/min/1.73 m^2 because of the inflammatory state of chronic kidney disease.

We calculated NLR by dividing the absolute neutrophil count by the absolute lymphocyte count. Also, PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count.

Furthermore, we assessed these patients' demographic characteristics, fasting blood glucose, and glycated hemoglobin (HbA1c).

Data Sources/Measurement

Data were extracted using the data files of patients referred to the diabetes clinic in the hospital. Patients' data were collected, baseline data (before empagliflozin) were compared with 3 months data (after empagliflozin).

Bias

The retrospective nature of this study resulted in several biases, one of which is the missed data that can affect the results. Thus, we excluded data from the files that had >50% missing data. Also, we did not have a control group or randomization so that confounders could affect the final analysis. For this purpose, we selected patients according to the inclusion criteria and determined some exclusion criteria to mitigate the effect of confounders. Also, to reduce information bias, the researcher who gathered data and the analyzer were blinded.

Study Size

To determine an appropriate sample size based on the Hattori et al study (10), we used G*Power software with the following parameters: a desired power (1 - Beta) of 0.8, an alpha error probability (Type 1 error) of 0.05 (indicating a 95% confidence level), and a 2-tailed t test. Based on these settings, the total sample size required was 40 participants.

Statistical Methods

Statistical analyses were performed using SPSS 23.0.0 software (IBM). We reported continuous variables with means ± standard deviation and categorical variables with percentages. A paired t test was used to compare biochemical and hematological parameters before and after empagliflozin. The statistically significant level was reported as $P < 0.05$.

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Results

This study's evaluation encompassed 40 patients diagnosed with type 2DM with a mean age of 56.9 ± 10.8 years. HbA1c levels averaged at 7.5 ± 1.5 percent. Other demographic and clinical characteristics are presented in Table 1. Laboratory data at baseline were reported in Table 2.

ESR and hs-CRP

After 12 weeks of observation, the results showed a notable decrease in ESR from 17.7 ± 15.7 to 14.7 ± 10.9 mm/hr ($P = 0.025$), signifying a significant reduction in inflammation levels. Conversely, the change in hs-CRP levels from 33 ± 30 to 32.8 ± 36.6 mg/L did not demonstrate statistical significance ($P = 0.936$) as illustrated in Figure 1.

Blood-Cell-Based Inflammatory Markers

Regarding blood-cell-based inflammatory markers, there was no substantial decrease in NLR values (1.8 ± 0.6 to 1.8 ± 0.6; $P = 0.962$). Notably, an increase in absolute lymphocyte count (ALC) from 2.4 ± 7.8 to 2.5 ± 7.4 109/L was observed, showing statistical significance ($P = 0.014$). Meanwhile, absolute neutrophil count (ANC) remained relatively unchanged (4.3 ± 1.5 to 4.5 ± 1.1 109/L; $P = 0.247$). It is worth mentioning that there was a noticeable trend toward a decrease in PLR values from 107.0 ± 33 to 100 ± 35.0 ($P = 0.053$), as depicted in Figure 2 and Table 2.

Table 1. Demographic and clinical characteristics of the study patients before treatment with empagliflozin

Variable	Baseline Data (n = 40)
Age (years)	56.9 (10.8)
Female, n (%)	21 (52.5)
IHD, n (%)	35 (87.5)
CKD, n (%)	38 (95)
HTN, n (%)	34 (85)
Weight, Kg	74.2 (12.6)
BMI, Kg/m^2	26.9 (3.4)

Quantitative data are presented as mean (SD). Qualitative data are reported as numbers (percent). IHD, ischemic heart disease; CKD, chronic kidney disease; HTN, hypertension; BMI, body mass index.

Serum Albumin

Moreover, following the treatment with empagliflozin,

Table 2. Comparison of biochemical and hemogram parameters of T2D patients before and after empagliflozin

Variable	Before empagliflozin (n = 40)	After empagliflozin (n = 40)	*P* value
FPG, mg/dl	172.35 (66.0)	137.22 (43.7)	<0.001**
HbA1c, %	7.5 (1.5)	6.4 (0.9)	<0.001**
Creatinine, mg/dl	1.06 (0.2)	1.04 (0.2)	0.275
ESR, mm/hr	17.7 (15.7)	14.7 (10.9)	0.025*
hs-CRP, mg/dl	3.3 (3.0)	3.2 (3.6)	0.936
Serum Albumin, g/dl	4.2 (0.3)	4.5 (0.3)	<0.001**
WBC, 10^9/l	7.1 (2.0)	7.4 (1.5)	0.091
Hb, g/dl	13.7 (1.6)	14.2 (1.7)	<0.001**
PLT, 10^3/mm^3	243.3 (50.7)	240.4 (54.2)	0.429
ALC, 10^3/mm^3	2.4 (7.8)	2.5 (7.4)	0.014*
ANC, 10^3/mm^3	4.3 (1.5)	4.5 (1.1)	0.247
NLR	1.8 (0.6)	1.8 (0.6)	0.962
PLR	107.0 (33.0)	100.0 (35.0)	0.053

Data are presented as mean (SD)
*$P < 0.05$, **$P < 0.001$.
FPG, fasting plasma glucose; ESR, erythrocyte sedimentation rate; hsCRP, high sensitively C-reactive protein; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

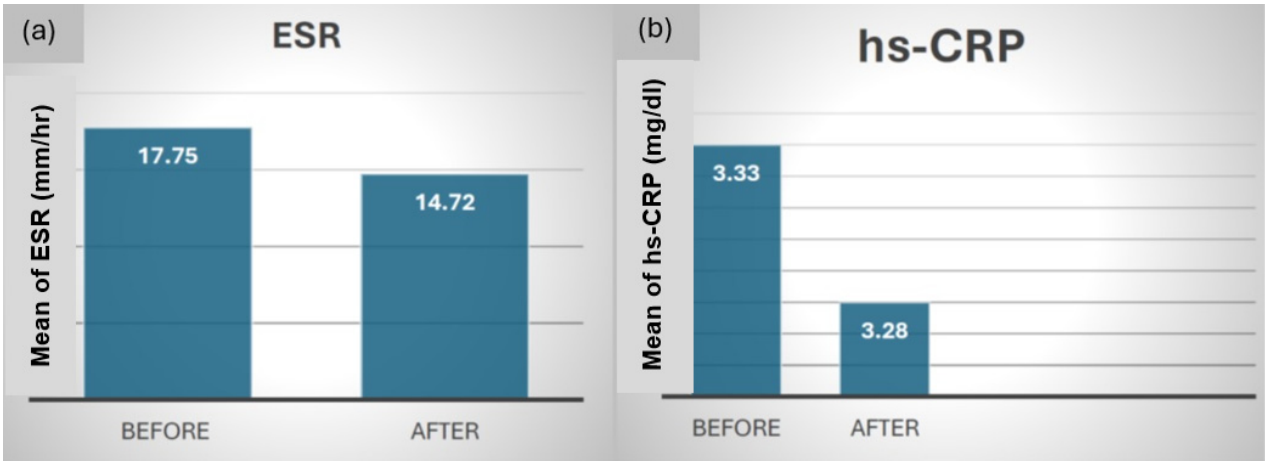

Figure 1. Empagliflozin affects erythrocyte sedimentation rate (ESR) and highly sensitive C-reactive protein (hs-CRP). (a) There was a significant ($P = 0.025$). (b) A decrease in hs-CRP after treatment with empagliflozin was observed, but it was not significant ($P = 0.936$). The numbers written in the boxes present the mean data.

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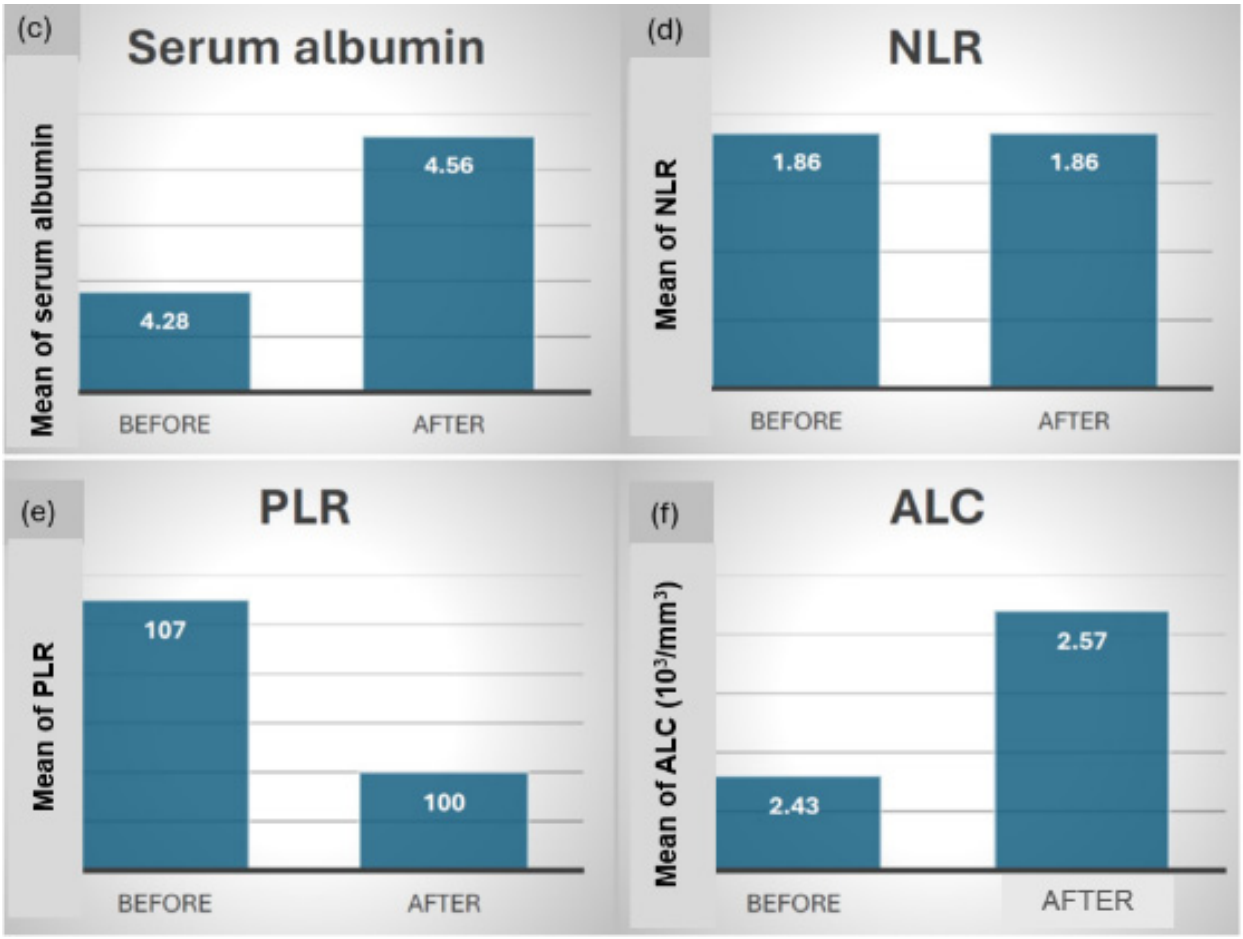

Figure 2. Empagliflozin effect on serum albumin, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and absolute lymphocyte count (ALC). (c) The serum albumin was increased significantly ($P < 0.001$). (d) NLR did not change ($P = 0.962$). (e) Decline in PLR was not significant ($P = 0.053$). (f) There was a significant rise in ALC ($P = 0.014$).

serum albumin levels substantially increased from 42.8 ± 3.4 to 45.6 ± 3.2 g/L ($P < 0.001$). This increment in serum albumin levels is a significant indicator of reduced inflammation levels over the treatment period.

Discussion

In our study, a significant decrease was found in the level of ESR after 12 weeks of empagliflozin treatment. Few studies were conducted on ESR and SGLT2 inhibitors. Andersen et al showed the anti-inflammatory effect of empagliflozin, which may contribute to the cardioprotective properties of empagliflozin. Also, they reported that empagliflozin increases erythropoiesis in patients with heart failure (11). One hypothesis is that increased red blood cells (RBCs) in the bloodstream can result in lower ESR levels, as the higher concentration of RBCs reduces their likelihood of settling quickly (12). In this regard, another study showed a significant decrease in ESR level after treatment with other SGLT2 inhibitors (dapagliflozin) in the setting of the peritoneal dialysis patients (13).

Even though there was a decrease in hsCRP, we could not detect a significant reduction in hsCRP. In contrast to our study, previous studies reported that empagliflozin can decrease hs-CRP. Hattini compared the effect of empagliflozin with placebo and showed that empagliflozin significantly decreased hs-CRP and suggested that the cardioprotective effect might be partly by this anti-inflammatory effect (10). Other studies showed similar positive results on the impact of empagliflozin on hs-CRP and other inflammatory markers (6, 14, 15). On the other hand, some results have shown nonsignificant changes in the level of hs-CRP after empagliflozin. In this regard, Reppo et al compared the anti-inflammatory effects of empagliflozin with semaglutide T2D patients, with 10 patients in each group. They reported a nonsignificant reduction in hs-CRP in both groups. Although this nonrandomized study had a small sample size, baseline characteristics were similar between the 2 groups (3). Also, Mohaghegh et al reported that in terms of hs-CRP level, no statistically significant difference was detected between different groups of antidiabetic drugs. However, the metformin group had a lower level of hs-CRP in comparison with metformin + empagliflozin group (9). Also, Benedikt et al reported that empagliflozin did not have any beneficial effect on inflammatory response after myocardial infarction compared with placebo (8). Hence, we can explain the nonsignificant decline in hs-CRP detected in our study through 2 factors. First, as shown

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by Hattori in another study, we did not find any significant decrease in hs-CRP levels after 3 months, but it could occur after a longer duration of follow-up. Second, pretreatment hs-CRP levels were within the normal range in our study so that results may differ in patients with higher baseline hs-CRP.

This study found a significantly increased serum albumin after treatment with empagliflozin. Serum albumin is a negative acute-phase protein caused by an inflammatory state. It can be associated with chronic disease or obesity. Thus, hypoalbuminemia is an indicator of the severity of inflammation (16, 17). We found only 1 study in the literature about the effect of SGLT2 inhibitors on serum albumin levels in the different settings. EMPEROR-Reduced Trial was conducted to detect the effects of empagliflozin on reduced ejection fraction heart failure patients with and without volume overload. They reported that treatment with empagliflozin was accompanied by minimal increases in serum albumin in both groups. However, only about one-half of these patients had a history of diabetes (2).

In our study, ALC was significantly increased without significant changes in ANC. After dividing neutrophil to lymphocyte count, we observed that NLR did not significantly decrease after 12 weeks of treatment with empagliflozin. Previous studies showed that NLR value is a marker of inflammation in patients with diabetes. Doğan showed a significant decrease in NLR in 194 patients with T2D after 12 weeks of treatment with empagliflozin, while ALC and ANC were not changed significantly in that study (7). In another study, there was a significant reduction in neutrophil count and NLR in the empagliflozin group. However, it was not different from the placebo group (12). Other studies showed no changes in NLR after treatment with empagliflozin (3) and dapagliflozin (17).

Further, we also showed a trend toward a significant decrease in PLR. This ratio was identified as an inflammatory state and can reveal shifts in platelet and lymphocyte counts. One study reported that PLR was decreased in patients treated with empagliflozin, but they did not find any evidence of differences between empagliflozin and placebo in that study (18).

There are some limitations to our study. These include nonclinical trial design and the small sample size. Despite these points, patients were compared with themselves, and similar baseline characteristics exist. We did not check all the inflammatory markers because it is not routine in clinical practice to check them; however, we tried to check some inexpensive and practical markers of inflammation in our study. Finally, there was multiple testing in statistical inference in this study that can be associated with an increased risk of false-positive findings.

To summarize, empagliflozin has shown some anti-inflammatory impact by reducing ESR and PLR while increasing serum albumin levels and ALC in patients with T2D. These anti-inflammatory effects of empagliflozin can be beneficial in preventing inflammatory-based events such as cardiovascular diseases, which are a leading cause of mortality in patients with T2D. Moreover, monitoring inflammatory markers can serve as an indicator of treatment effectiveness in T2D patients. Further studies are needed to explore the long-term effects of empagliflozin on inflammation in larger populations.

Conclusion

In adults with T2D, empagliflozin showed anti-inflammatory effects by lowering ESR and PLR and raising serum albumin and lymphocyte count.

Authors' Contributions

Design and conceptualization: H.S. Data curation: all authors. Formal analysis: H.S., A.G., D.E., A.Z., Z.B., and H.C. Investigation: all authors. Methodology: all authors. Project administration: H.S., A.G., and Z.B. Supervision: H.S. and A.Z. Validation: H.S., A.Z., D.E., H.C., and A.G. Writing original draft: H.C. Review and editing: all authors.

Ethical Considerations

This study was approved by the Ethics Committee of the Iran University of Medical Sciences (ethics code.R.IUMS.FMD.REC.1402.044) and was conducted under the rules of the Declaration of Helsinki. Written informed consent for participation was not applied in this study.

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Conflict of Interests

The authors declare that they have no competing interests.

References

1. Ellulu MS, Samouda H. Clinical and biological risk factors associated with inflammation in patients with type 2 diabetes mellitus. BMC Endocr Disord. 2022;22:1-0.
2. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. Immunity. 2022;55:31-55.
3. Reppo I, Jakobson M, Volke V. Effects of Semaglutide and Empagliflozin on Inflammatory Markers in Patients with Type 2 Diabetes. Int J Mol Sci. 2023;24:5714.
4. Elimam H, Abdulla AM, Taha IM. Inflammatory markers and control of type 2 diabetes mellitus. Diabetes Metab Syndr. 2019;13:800-4.
5. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis K, et al. The impact of SGLT2 inhibitors on inflammation: A systematic review and meta-analysis of studies in rodents. Int Immunopharmacol. 2022;111:109080.
6. Iannantuoni F, M. de Marañon A, Diaz-Morales N, Falcon R, Bañuls C, Abad-Jimenez Z et al. The SGLT2 inhibitor empagliflozin ameliorates the inflammatory profile in type 2 diabetic patients and promotes an antioxidant response in leukocytes. J Clin Med. 2019;8:1814.
7. Doğan M. The effect of empagliflozin on monocyte high-density lipoprotein ratio in patients with type 2 diabetes mellitus. ACMJ. 2022;4:255-9.
8. Benedikt M, Mangge H, Aziz F, Curcic P, Pailer S, Herrmann M, et al. Impact of the SGLT2-inhibitor empagliflozin on inflammatory biomarkers after acute myocardial infarction-a post-hoc analysis of the EMMY trial. Cardiovasc Diabetol. 2023;22:166.
9. Mohaghegh P, Rezvanfar MR, Jalali-Mashayekhi F, Amerei Z, Hosseinzadeh M. Comparison of inflammatory markers in type 2 diabetic patients treated with empagliflozin, metformin, and sulfonylurea. J Shahrekord Univ Med Sci. 2023;25:189-93.
10. Hattori S. Anti-inflammatory effects of empagliflozin in patients with type 2 diabetes and insulin resistance. Diabetol Metab Syndr. 2018;10:93.
11. Andersen C, Omar M, Glenthoej A, Fassi DE, Moeller HJ, Styrishave

[DOI: 10.47176/mjiri.38.105]

B, et al. Direct effects of empagliflozin on erythropoiesis in heart failure: data from the Empire HF trial. Eur Heart J. 2022;43:544-968.
12. Goodnough LT, Skikne B, Brugnara C. Erythropoietin, iron, and erythropoiesis. Blood. 2000;96:823-33.
13. Alhwiesh AK, Abdul-Rahman IS, Nasreldin MA, Mohammed AM, Al-Oudah S, Al-Thwainy R. The use of SGLT2 inhibitors in peritoneal dialysis patients: a shade of light on dapagliflozin. Arch Nephrol Urol. 2022;5:1-8.
14. Gohari S, Reshadmanesh T, Khodabandehloo H, Karbalaee-Hasani A, Ahangar H, Arsang-Jang S, et al. The effect of EMPAgliflozin on markers of inflammation in patients with concomitant type 2 diabetes mellitus and Coronary ARtery Disease: the EMPA-CARD randomized controlled trial. Diabetol Metab Syndr. 2022;14:1-3.
15. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. JPEN. 2019;43:181-93.
16. Balcioglu YH, Kirlioglu SS. C-reactive protein/albumin and neutrophil/albumin ratios as novel inflammatory markers in patients with schizophrenia. Psychiatry Investig. 2020;17:902.
17. Baş S, Türkmen FM. Changes in neutrophil-to-lymphocyte ratio following treatment with dapagliflozin in patients with type 2 diabetes mellitus. Gülhane Tip Dergisi. 2022;64:217.
18. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med. 2019;39:345.

[DOI: 10.47176/mjiri.38.105]