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Original Article

Comparison of inflammatory markers in type 2 diabetic patients treated with empagliflozin, metformin, and sulfonylurea

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Abstract

Background and aims: The present study aimed to compare the levels of the inflammatory biomarkers of fibrinogen and high-sensitivity C-reactive protein (hs-CRP) among type 2 diabetic patients treated with empagliflozin and other hypoglycemic drugs.

Methods: This cross-sectional study was performed on 90 patients with type 2 diabetes (≥30 years) receiving empagliflozin, metformin, and sulfonylurea who were referred to the diabetes clinics affiliated with Arak University of Medical Sciences. After obtaining consent to participate in the study, the patients were categorized into the treatment groups of metformin, metformin + empagliflozin, or metformin + sulfonylurea, and their characteristics and hypoglycemic drugs were recorded in the information checklist. The data were analyzed in SPSS 16 statistical software.

Results: The fibrinogen level was minimized in the metformin + empagliflozin group, although the three groups were not significantly different in this regard ($P=0.382$). Based on the results, the parameter was higher in the individuals with ischemic heart disease, while a lower level was found among those treated with a lipid-lowering agent. In terms of hs-CRP level, no statistically significant difference was observed among the three groups, although the metformin group had a lower level ($P=0.522$).

Conclusion: The minimum fibrinogen and hs-CRP levels were related to the metformin + empagliflozin and metformin groups, respectively. Further, several factors such as comorbidities and other consumed drugs could affect the concentration of inflammatory factors. Thus, it is suggested that clinical trials should be conducted in this respect.

Keywords: Empagliflozin, Fibrinogen, High-sensitivity C-reactive protein, Inflammatory factors, Sodium-dependent glucose cotransporter 2 inhibitors, Type 2 diabetes

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Introduction

According to the World Health Organization, diabetes is known as the most common endocrine disease in the world, the prevalence of which is growing in various communities due to increased obesity incidence, decreased physical activity, and aging (1). Type 2 diabetes (T2D) is a metabolic disorder, characterized by tissue resistance to insulin and reduced insulin secretion. Following disease diagnosis, treatment begins through lifestyle modification and oral drug administration (1). In this regard, sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors are considered one class of oral drugs. Given that SGLT2 reabsorbs most of the glucose excreted in the urine, the inhibition of its function leads to glucosuria and declined glucose levels in T2D patients (2,3). The medications are associated with a low risk of hypoglycemia and help lose weight and diminish blood pressure (4-7). Dapagliflozin, canagliflozin, and empagliflozin are among the drugs in this class (8-10). They are prescribed in a usual daily dose of 10 mg, the amount of which can be elevated up to 25 mg once a day. Several studies have revealed the effect of this group of medications on decreasing cardiovascular consequences among individuals with T2D. Based on the results of some reviews, empagliflozin reduces the risk of these consequences due to its antisclerotic effects, as well as hemodynamic activities such as a decline in blood pressure, intravascular volume, and osmotic diuresis. In addition, metabolic (e.g., increased cardiac fuel) and hormonal (e.g., more glucagon release) effects may be a reason for diminishing cardiovascular events after consuming this drug. The class can play a role in decreasing cardiovascular consequences and diabetes complications by lowering the value of inflammatory biomarkers such as *tumor necrosis factor-alpha* (TNF-α),

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interleukin IL-6, C-reactive protein (CRP), and leptin (11,12). However, few data are available regarding the effect of medications on inflammatory biomarkers such as high-sensitivity CRP (hs-CRP) in human samples (11).

Given the limited relevant studies, some researchers focused on comparing the effect of the drug and other oral hypoglycemic medications on reducing the concentration of inflammatory biomarkers (11). However, no study, to the best of our knowledge, has been so far performed in Iran in this regard. Therefore, the present study compared inflammatory factor levels among the patients receiving this medication and other oral hypoglycemic ones.

Materials and Methods

This comparative cross-sectional study was conducted among type 2 diabetic individuals referred to the diabetes clinics affiliated with Arak University of Medical Sciences. To this end, 90 individuals suffering from T2D (30 years), who had been continuously treated with metformin, metformin + empagliflozin, or metformin + sulfonylurea for the past two months and exhibited normal renal function, were selected through using the convenience sampling method. Those receiving metformin + empagliflozin, metformin, and metformin + sulfonylurea were assigned to groups 1-3, respectively. After getting informed consent to participate in the current study, the patients were referred to the laboratory under contract with the university with a test request form for evaluating the amount of blood sugar and inflammatory biomarkers (fibrinogen and hs-CRP). Additionally, the background characteristics and hypoglycemic drugs of the individuals were included in their information checklist. The presence of a relationship between the blood concentrations of inflammatory biomarkers with the type of used drug, as well as age, gender, and comorbidities, underwent examination. Ethical considerations such as having informed consent to participate, withdrawing from the study optionally, and maintaining information confidentiality were observed in all stages of the study.

Further, the patient tests were free, the expenses of which were covered by the dissertation grant. The sample size was calculated at 30 cases in each group using G*Power software with 80% power, α (type 1 error) = 0.05, and based on the information (CRP level in SGLT2-I vs. non-SGLT-I users was 3.1 vs. 9.9 and size effect = 0.8) of the study by Paolisso et al (13). The total sample size was equal to 90 cases. The inclusion criteria were the age of 30 years and above, as well as suffering from T2D, consuming metformin, metformin + empagliflozin, or metformin + sulfonylurea continuously for the past two months, and having a normal renal function. However, those unwilling to participate in the study were excluded. The kits provided by Mahsa Yaran and Monobind Companies were applied to determine the levels of fibrinogen and hs-CRP, respectively. The qualitative data were reported as numbers and percentages, while the normal and skewed quantitative ones were expressed as means ± standard deviations (SD), and medians and interquartile ranges, respectively. The normality of quantitative variables was measured based on the Kolmogorov-Smirnov and Shapiro-Wilk tests, and histogram diagram. Furthermore, the mean values of age, diabetes duration, and blood sugar were compared among the three groups by using the one-way ANOVA (normal parameters) and Kruskal-Wallis analyses (skewed variables). ANCOVA test was used for the comparison of inflammatory biomarkers among the three groups by adjusting the effect of fasting blood sugar (FBS) and glycated hemoglobin (HbA1c). To compare the mean concentrations of inflammatory biomarkers between males and females, as well as the patients with underlying disease, an independent t-test and Mann-Whitney test were employed for normal and skewed parameters, respectively. The relationship between the quantitative variables of age and disease duration with inflammatory biomarker levels was assessed by using Pearson's correlation coefficient. Finally, the data were analyzed in SPSS 16 statistical software at the type I error level of 5%.

Results

In this study, 90 type 2 diabetic patients with a mean age of 55.12 ± 11.21 were evaluated in three treatment groups metformin, metformin + empagliflozin, and metformin + sulfonylurea. Table 1 summarizes the mean age of the patients by the treatment groups, reflecting no statistically significant difference between the groups ($P = 0.467$). The mean ± SD and median of diabetes duration were equal to 6.41 ± 6.75 and 5 years, respectively, although the groups were not significantly different ($P = 0.184$). In addition, the known comorbidities were detected in 67 (74.4%) patients, and 17 (18.9%) and 73 (81.1%) individuals were males and females, respectively.

Based on the results (Table 1), a statistically significant difference was found among the three groups with respect to mean FBS and HbA1c ($P = 0.001$). The patients in the metformin + sulfonylurea group had higher FBS and HbA1c, followed by those in metformin + empagliflozin and metformin groups, respectively.

The mean fibrinogen levels were not significantly different among the three groups ($P = 0.382$). Regarding this parameter, the maximum and minimum values were related to the metformin + sulfonylurea and metformin + empagliflozin groups, respectively. Further, the results indicated no significant difference in the three groups in terms of the level of hs-CRP ($P = 0.522$).

The values of fibrinogen and hs-CRP by gender, as well as the history of hypertension and ischemic heart disease and consumption of aspirin and hypolipidemic medications, are presented in Table 2. Based on the data, no statistically significant difference was observed in the mean concentration of fibrinogen and median of hs-CRP between the two genders, as well as individuals with and

Table 1. Comparison between age, disease duration, inflammatory markers, and blood sugar in type 2 diabetic patients receiving oral hypoglycemic medications

Variables Mean (SD)	All Patients	Metformin	Metformin + empagliflozin	Metformin + sulfonylurea	*P*value
Age (y)	55.12 (11.21)	53.33 (11.64)	55.10 (11.77)	56.93 (10.25)	0.467
Diabetes duration (y)	5 (7)	4.50 (6)	5.50 (7)	7 (8)	0.184
FBS	156.16 (45.77)	135.03 (28.79)	155.26 (45.66)	178.23 (50.48)	0.001
HbA1C	7.40 (1.69)	6.74 (0.95)	7.03 (1.26)	8.43 (2.14)	0.001
Hs-CRP (mg/L)	0.71 (0.74)	0.62 (0.44)	0.89 (1.48)	0.74 (0.80)	0.522*
Fibrinogen (mg/L)	288.53 (44.60)	285.93 (41.22)	280.86 (41.95)	298.80 (49.68)	0.382*

Note. SD: Standard deviation; FBS: Fasting blood sugar; HbA1C: Glycated hemoglobin; Hs-CRP: High-sensitivity C-reactive protein.
* ANCOVA: Analysis of covariance.
All variables are presented with Mean (SD).

Table 2. Comparison of inflammatory biomarkers among type 2 diabetic individuals by gender, comorbidities, and used drugs

Variables		hs-CRP	*P* value	Fibrinogen	*P* value
Gender	Female	1.82 (2.60)	0.734	276.67 (42.46)	0.415
	Male	1.07 (0.74)		296.52 (53.52)	
Hypertension	Yes	1.43 (1.78)	0.569	298.18 (47.54)	0.128
	No	1.77 (2.57)		284.20 (42.37)	
Ischemic heart diseases	Yes	1.63 (1.58)	0.044	311.80 (52.88)	0.080
	No	1.65 (2.39)		285.62 (42.95)	
Aspirin use	Yes	1.43 (1.78)	0.768	290.70 (54.31)	0.747
	No	1.76 (2.54)		287.45 (39.33)	
Anti-hyperlipidemia agents	Yes	1.40 (1.80)	0.312	286.40 (46.08)	0.481
	No	2.25 (3.22)		293.76 (41.11)	

Note. Hs-CRP: High-sensitivity C-reactive protein. hs-CRP and fibrinogen are presented with Mean (SD)

without hypertension. The two parameters were lower among the patients treated with hypolipidemic drugs than the others but the difference was statistically insignificant. Furthermore, the subjects with ischemic heart disease had higher mean fibrinogen levels, although this was not statistically significant ($P = 0.080$).

The results revealed no statistically significant correlation between age and disease duration with the number of inflammatory factors. However, FBS was positively and significantly related to the fibrinogen level ($P = 0.033$), thus greater FBS enhanced the concentration of this inflammatory factor, while no significant relationship was found between FBS and hs-CRP ($P = 0.605$). Finally, there was no statistically significant correlation between fibrinogen ($P = 0.119$) and hs-CRP ($P = 0.129$) with HbA1c.

Discussion

The present study compared the levels of fibrinogen and hs-CRP among 90 type 2 diabetic individuals assigned to three treatment groups. Based on the results, no statistically significant difference was observed among the three groups regarding mean fibrinogen level, although the treatment with metformin + empagliflozin led to a lower value. Additionally, hs-CRP concentrations were not significantly different among the groups. Currently, it is well-proven that high blood sugar is associated with vascular complications and inflammation in diabetes (14). Antidiabetic medications can relieve inflammation by reducing hyperglycemia (14). Thus, a decrease in inflammation and inflammatory factor levels could cause fewer diabetes complications such as cardiovascular ones, and enhance the control of the disease (13,14). The recent antidiabetic drugs play a well-known role in lowering inflammatory factor concentration (13-15). The SGLT2 inhibitor medications (e.g., empagliflozin) could contribute to a decrease in cardiovascular consequences and diabetes complications (16,17) by decreasing the amounts of inflammatory biomarkers such as TNF-α, IL-6, CRP, and leptin (11,12,16-18). The results of a systematic review indicated that SGLT2 drugs could diminish the values of CRP, IL-6, and TNF-α, and this variation in the CRP level is independent of the effect of the medications on the HbA1c concentration (19). However, the exact mechanism of action of the drugs for reducing inflammation in T2D is unclear, and inflammation improvement appears to be independent of an increase in blood sugar control (19).

Metformin can be addressed as another oral antidiabetic medication. Today, it is considered the first line of diabetes treatment, enhancing diabetes control by producing a lower amount of hepatic glucose and promoting insulin sensitivity. According to the US Diabetes Prevention Study, this drug results in diminishing CRP levels in individuals suffering from impaired glucose tolerance (20). The results of recent research have suggested the anti-inflammatory effect of metformin on patients with T2D (21). Some researchers, in a systematic review, reported CRP as the highest effect of metformin on lowering inflammatory factor levels in type 2 diabetic individuals, thus the value of this factor diminishes significantly (21). It seems that the role of empagliflozin in decreasing the cardiovascular and renal consequences and complications of diabetes is attributed to the higher effect on inflammatory biomarkers other than CRP. However, this hypothesis should be proven by conducting clinical trial studies.

In the present study, no statistically significant difference was found in the levels of fibrinogen and hs-CRP between diabetic patients with hypertension and another group. However, the mean ± SD of fibrinogen was more among those developing ischemic heart disease

compared to the others. Researchers have introduced the greater value of this factor in diabetic individuals as a reason for more cardiovascular consequences and other diabetes complications (22-24).

Further, the mean ± SD of fibrinogen and hs-CRP was insignificantly less in patients receiving hypolipidemic medications compared to that of another group. The results of several studies have proven the effective role of statin drugs in decreasing inflammatory factors, and consequently preventing and decreasing cardiovascular diseases among individuals with T2D (25,26).

Furthermore, a positive significant relationship was detected between FBS and fibrinogen so that the concentration of this factor was elevated by increasing FBS. Given that diabetic patients are prone to thrombotic events, the administration of antidiabetes drugs controlling inflammatory and thrombogenic status is essential for reducing thrombogenic status, losing weight, and lowering blood hyperlipidemia (27). The results of the present study represented a significant difference between the three groups in terms of the mean FBS and HbA1c. Finally, the two parameters were lower in the individuals treated with metformin, metformin + empagliflozin, and metformin + sulfonylurea, respectively.

In this cross-sectional study, it was impossible to investigate and control the effect of some confounding factors, including the body mass index of people, which can affect the results. Therefore, it is recommended to consider this factor in future studies. The present study failed to compare the concentrations of inflammatory factors before and after taking oral hypoglycemic drugs. The comparison between the effects of each class of oral hypoglycemic medications on inflammatory factor levels requires randomized clinical trials, which were impossible due to cost (expensiveness of inflammatory tests) and time constraints. In addition, the cost of interventional studies is extremely high since empagliflozin is expensive and not under insurance coverage. The amount of hs-CRP, one of the inflammatory factors, elevates in many infectious and inflammatory diseases such as COVID-19 (28). In the present study, none of the patients had COVID-19, although analyzing and comparing the results of this factor necessitates extensive clinical trials considering all of the effective and interfering factors and diseases.

Suggestions for future research

Extensive randomized clinical trials with a high sample size and adequate research budget are needed to compare the exact effect of various oral hypoglycemic drugs on the concentration of inflammatory factors, especially hs-CRP. Given the effectiveness of several parameters on inflammatory factor levels, such factors are recommended to be considered in future clinical trial studies.

Conclusion

The results revealed that the metformin + empagliflozin group had the minimum mean concentration of fibrinogen, although no statistically significant difference was found among the three groups. Further, the groups were not significantly different with respect to the mean hs-CRP level.

Acknowledgments

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Authors' Contribution

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Competing Interests

The authors declare no conflict of interests in this paper.

Ethical Approval

This study was approved by the Ethics Committee of Arak University of Medical Sciences with the ethics code of IR.ARAKMU.REC.1398.290.

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