

# Effect of empagliflozin use on monocyte high-density lipoprotein ratio and plasma atherogenic index in obese and non-obese type 2 diabetic patients

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**Abstract. – OBJECTIVE:** Diabetes mellitus (DM) is a metabolic disorder marked by hyperglycemia, caused by impaired insulin secretion and activity. Chronic inflammation holds a significant role in the development, progression, and complications of DM and obesity. There are publications reporting that the monocyte/high-density lipoprotein (HDL)-C ratio (MHR) and plasma atherogenic index (PAI) could be used as indicators of systemic inflammation. In the present study, we aimed to explore the effect of empagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), on MHR and PAI in obese and non-obese type 2 diabetes mellitus (T2DM) patients.

**PATIENTS AND METHODS:** A total of 125 patients who presented to the outpatient clinics of Tokat Gaziosmanpasa University Hospital between January 2019 and January 2023 with a diagnosis of T2DM and were started on 25 mg empagliflozin and used for a minimum of 24 weeks were included in the study. The patients' age varied between 18-75 years, were without chronic liver disease, chronic renal failure, infection, or inflammatory disease, and were not on drugs affecting bone marrow. The patients were categorized into two groups, obese and non-obese, according to their body mass index (BMI). The data obtained were statistically analyzed using the IBM SPSS Statistics 25 software package.

**RESULTS:** The mean age of the patients was  $57.5 \pm 10.9$  years. Of the patients, 59.2% (n = 74) were female, and 40.8% (n = 51) were male. The mean HbA1c percentage was  $8.99 \pm 2.18\%$  prior to empagliflozin treatment and significantly decreased to  $7.68 \pm 1.80\%$  after empagliflozin use ( $p < 0.05$ ). The mean monocyte HDL-C ratio (MHR) pre- and post-empagliflozin treatment was  $16.22 \pm 6.31$  and  $13.77 \pm 5.29$ , respectively, and these values significantly differed from each other ( $p < 0.05$ ). The mean plasma atherogenic index (PAI) of the patients before empagliflozin treatment was  $0.62 \pm 0.28$ , whereas, after the treatment, it significantly reduced to  $0.52 \pm 0.27$  ( $p < 0.05$ ). While MHR and PAI statistically significantly de-

creased with the use of empagliflozin, there was no difference between the obese and non-obese patient groups in terms of MHR and PAI results.

**CONCLUSIONS:** Studies in the literature show that the decrease in MHR and PAI leads to a decline in inflammation. MHR and PAI are inexpensive and practical markers to assess cardiovascular disease risk and inflammation in diabetic patients. This finding indicates that MHR and PAI can be used as inflammation markers in patients on empagliflozin treatment.

*Key Words:*

Empagliflozin, Monocyte/HDL ratio (MHR), Plasma atherogenic index (PAI), Type 2 diabetes mellitus (T2DM).

## Introduction

Diabetes is a chronic metabolic disease where the body cannot adequately utilize carbohydrates, fats, and proteins because of inadequate insulin secretion or defect in insulin action and necessitates continuous medical care<sup>1</sup>. The International Diabetes Federation (IDF) estimates that about 425 million people, or 8.8% of adults aged 20-79 years, have diabetes worldwide and that this figure is projected to reach 629 million by the year 2045<sup>2</sup>. When not managed properly, all diabetes types can lead to complications that affect various parts of the body, causing frequent hospitalization and premature mortality<sup>2,3</sup>.

Obesity is associated with many diseases and abnormalities, including type 2 diabetes<sup>4</sup>, dyslipidemia<sup>5</sup>, cardiovascular diseases<sup>6</sup>, hypertension<sup>7</sup>, certain types of cancer<sup>8</sup>, pneumological<sup>9</sup>, nephrological<sup>10</sup>, skeletal muscle<sup>11</sup>, rheumatologic<sup>12</sup>, dermatologic and neuropsychologic complications<sup>13</sup>. Moreover, there is also an association between

obesity and premature mortality. Obesity, particularly the dysfunctional visceral adipose tissue (VAT), holds a significant role in the development of numerous metabolic abnormalities such as insulin resistance, hyperinsulinemia, glucose intolerance, atherogenic dyslipidemia [high triglyceride and apolipoprotein B levels, increased proportion of small, dense low-density lipoprotein (LDL) particles, low high-density lipoprotein (HDL) cholesterol levels]. There are also reports showing that obesity is associated with low-grade inflammation. The association of obesity with type 2 diabetes mellitus (T2DM) has been widely acknowledged for a long time and accounts for the high prevalence of T2DM.

T2DM is linked to various vascular complications, which are classified into microvascular complications (diabetic kidney disease, retinopathy, and neuropathy) and macrovascular complications (coronary artery, cerebrovascular, and peripheral vascular diseases). The primary objectives in treating T2DM patients are to attain optimal glycemic control, reduce body weight and inhibit vascular and target organ damage<sup>14</sup>. Novel antidiabetic drugs such as sodium-glucose co-transporter 2 (SGLT2) inhibitors offer a new approach to prevent or mitigate the complications arising from insulin resistance and hyperglycemia<sup>15</sup>. SGLT2 inhibitors are effective antihyperglycemic agents that prevent the reabsorption of glucose in the kidney's proximal tubules by the induction of glycosuria and the improvement of blood glucose levels. They may also aid in the reduction of body weight *via* calorie loss. Many literature reports<sup>16</sup> have demonstrated that SGLT2 inhibitors are linked to lower cardiovascular mortality and morbidity, including vascular diseases and heart failure. Furthermore, they have also been demonstrated to possess positive reno-metabolic effects<sup>17</sup>. A cardiovascular outcome trial reported that the SGLT2 inhibitor empagliflozin was superior to standard antidiabetic therapy in reducing the frequency of major adverse cardiovascular events, mortality, and hospitalization attributed to heart failure<sup>18</sup>. SGLT2 inhibitor therapy has been correlated with a decline in serum triglyceride levels, an elevation in HDL cholesterol. Besides, a small increase in LDL cholesterol levels with the use of SGLT2 inhibitor has been observed.

The anti-inflammatory and antioxidant effects of HDL-C, as well as the monocyte/HDL-C ratio (MHR) based on the pro-inflammatory effect of monocytes, reflect inflammation and oxidative

stress. Numerous studies<sup>19-20</sup> have employed MHR to explore the potential involvement of inflammation and atherosclerosis in the etiopathogenesis of cardiovascular and cerebrovascular diseases. In the literature, it was shown that MHR is a significant indicator of inflammation in conditions such as atherosclerotic heart disease, chronic kidney disease, etc., and also an important biomarker in diabetic patients, especially in the occurrence of microvascular complications such as nephropathy. Plasma atherogenic index (PAI) is considered an independent determinant of cardiovascular disease (CVD). PAI is calculated by the logarithm of the ratio of TG to HDL and is an indirect indicator of small particulate LDL<sup>21</sup>. Our study aimed to explore the effect of empagliflozin use on MHR and PAI, which are used as markers of inflammation in cardiovascular disease and glycemic control, in obese and non-obese type 2 diabetic patients who were started on empagliflozin.

## Patients and Methods

The study was conducted after obtaining ethical approval from Tokat Gaziosmanpaşa University Clinical Non-interventional Clinical Researches Ethics Committee (Date: 08.09.2022, Decision No.: 22-KAEK-183). All study procedures were conducted, complying with the ethical guidelines and principles stated in the Declaration of Helsinki. Patients who presented to our internal medicine outpatient clinic with a diagnosis of T2DM and were started on empagliflozin 25 mg and used it for a minimum of 24 weeks between 01.01.2019 and 01.10.2022, were evaluated retrospectively. Patients aged 18-75 years, who had not used empagliflozin before and who received 25 mg empagliflozin treatment for at least 24 weeks were included in the study. Patients with type 1 DM, malignant diseases, chronic organ failure, history of rheumatological diseases, vasculitis, corticosteroid therapy, acute or chronic heart failure, splenomegaly or hypersplenism, initiation of antihyperlipidemic, omega-3, vitamin D and vitamin E medication within 1 month and history of infection (tuberculosis, malaria, Brucella, urinary infection) that progress with inflammation causing an elevated monocyte count were excluded from the study. Blood samples were taken from the patients after 10-12 hours of fasting. The evaluation included data on empagliflozin values before treatment initiation and at least 24 weeks after treatment initiation. HbA1c, HDL-C,

LDL-C, triglycerides, hemogram, and biochemistry parameters were analyzed. Based on the body mass index, individuals with a BMI less than 30 were considered non-obese, and those with a BMI of 30 or higher were considered obese. Plasma atherogenic index (PAI), monocyte HDL-C ratio (MHR) and body mass index were calculated with the formulas given below:

PAI:  $\text{Log}_{10} [\text{TG}/\text{HDL-C}]$

MHR:  $[\text{Monocyte} (10^3/\text{mm}^3)/(\text{HDL-C})]$

BMI: weight (kg) divided by the square of height ( $\text{m}^2$ )

### Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) software was utilized to perform all statistical analyses. Descriptive, graphical, and statistical methods were employed to examine whether the scores obtained from each continuous variable were normally distributed. The normality of continuous variables was checked by the Kolmogorov-Smirnov test. In addition to performing descriptive statistical methods (number, percentage, mean, standard deviation, etc.), the Mann-Whitney U test was utilized to compare quantitative data between the groups. The Wilcoxon signed-ranks test was employed to test the differences in repeated measurements. The results obtained were statistically evaluated at the 95% confidence interval and  $p < 0.05$  significance level.

## Results

### Patient Characteristics

A total of 125 patients with T2DM, 74 females and 51 males, with an overall mean age of 57.5 (SD  $\pm$  10.9, range 18-80) years, were enrolled in the study. Among the patients, 100 (80%) had a chronic disease, and 79 (63%) had obesity (BMI:  $\geq$  30). As a chronic disease, 65 (52%) patients had hypertension (HT), 43 (34%) had hyperlipidemia (HL), and 35 (28%) had coronary artery disease (CAD). All of the patients (100%) were treated with 25 mg empagliflozin for a mean of 30.7 (SD  $\pm$  4.9) weeks; 51 (40.8%) received statin and insulin therapy, and 74 were on one or more oral antidiabetic drugs (Table I).

### Change in Laboratory Parameters After Empagliflozin Use

In the obese and non-obese patients included in our study, empagliflozin treatment resulted

**Table I.** Patient characteristics.

Variables (N = 125)	n (%)
<b>Age mean (SD)</b>	57.5 (10.9)
<b>Gender</b>	
Male	51 (40.8)
Female	74 (59.2)
<b>Chronic disease n (%)</b>	100 (80)
HT	65 (52)
HL	43 (34.4)
CAD	35 (28)
<b>BMI n (%)</b>	
< 30	46 (36.8)
$\geq$ 30	79 (63.2)
<b>Empagliflozin use time (week), mean (SD)</b>	30.7 (4.9)
<b>Statin</b>	
Yes	51 (40.8)
No	74 (59.2)
<b>Insulin + OAD</b>	
Yes	51 (40.8)
Only OAD	74 (59.2)

SD: Standard deviation, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary Artery Disease, BMI: Body Mass Index, OAD: Oral Antidiabetic Drugs.

in a statistically significant mean decrease in glucose level (41.21, 95% CI: -57.00; -25.43 mg/dL), HbA1c level (1.32; 95% CI: -1.74; -0.90%), total cholesterol level (10.87; 95% CI: -21.27; -0.47 mg/dL), triglyceride level (37.87; 95% CI: -58.29; -17.46 mg/dL), monocyte count (81.36; 95% CI: -110.89; -51.83  $10^3/\text{mm}^3$ ) MHR level (2.44; (95% CI: -3.50; -1.39) and PAI level (0.10; 95% CI: -0.14; -0.06) ( $p < 0.001$  and  $p < 0.05$ ). However, the BUN level significantly increased (5.12; 95% CI: 1.98; 8.25 mg/dL) ( $p < 0.01$ ) after empagliflozin treatment. No statistically significant difference was detected for other laboratory parameters with the use of empagliflozin ( $p > 0.05$ ) (Table II). The mean change in glucose, HbA1c, triglyceride, monocyte, MHR, PAI, and BUN levels did not demonstrate any significant difference between the obese and non-obese patient groups ( $p > 0.05$ ). The non-obese patients had decreased levels of potassium ( $p = 0.046$ ) and total cholesterol (mg/dl) ( $p < 0.001$ ) after empagliflozin treatment. The decrease in potassium, total cholesterol (mg/dl), and calcium levels after empagliflozin use was significantly higher in the non-obese patients than in the obese patients ( $p < 0.01$  and  $p < 0.05$ ) (Table III).

**Table II.** Comparison of laboratory parameters before and after empagliflozin use.

Variables	Empagliflozin			p-value <sup>a</sup>
	Before Mean ± SD	After Mean ± SD	Difference Mean (95% CI)	
Glucose (mg/dL)	199.42 ± 83.37	158.21 ± 71.97	-41.21 (-57.00; -25.43)	< 0.001*
HbA1c (%)	8.99 ± 2.18	7.68 ± 1.80	-1.32 (-1.74; -0.90)	< 0.001*
BUN (mg/dl)	22.50 ± 15.51	27.62 ± 19.46	5.12 (1.98; 8.25)	0.002*
Creatinine (mg/dl)	0.82 ± 0.21	0.85 ± 0.28	0.03 (-0.01; 0.06)	0.125
Sodium (mEq/L)	138.61 ± 2.76	139.10 ± 2.58	0.49 (-0.07; 1.05)	0.086
Potassium (mEq/L)	4.54 ± 0.43	4.53 ± 0.44	-0.01 (-0.09; 0.07)	0.837
Calcium (mg/dL)	9.66 ± 0.44	9.68 ± 0.46	0.02 (-0.08; 0.12)	0.690
Hemoglobin (g/dL)	13.84 ± 1.89	14.14 ± 2.24	0.30 (-0.06; 0.66)	0.104
Hematocrit (%)	41.64 ± 5.06	42.05 ± 5.46	0.41 (-0.27; 1.09)	0.238
Total Cholesterol (mg/dl)	195.84 ± 52.76	184.97 ± 57.25	-10.87 (-21.27; -0.47)	0.041*
LDL-C (mg/dl)	123.85 ± 41.16	124.73 ± 33.86	0.88 (-4.10; 5.86)	0.727
HDL-C (mg/dl)	45.45 ± 12.16	47.45 ± 13.58	2.00 (-0.22; 4.23)	0.077
ALT (IU/L)	23.61 ± 17.23	21.73 ± 11.23	-1.88 (-4.79; 1.04)	0.205
AST (IU/L)	21.89 ± 14.25	20.36 ± 9.13	-1.53 (-3.82; 0.75)	0.186
Triglycerides (mg/dl)	210.72 ± 127.05	172.85 ± 111.84	-37.87 (-58.29; -17.46)	< 0.001*
Monocytes (10 <sup>3</sup> /mm <sup>3</sup> )	689.44 ± 162.35	608.08 ± 155.24	-81.36 (-110.89; -51.83)	< 0.001*
MHR	16.22 ± 6.31	13.77 ± 5.29	-2.44 (-3.50; -1.39)	< 0.001*
PAI	0.62 ± 0.28	0.52 ± 0.27	-0.10 (-0.14; -0.06)	< 0.001*

\* $p < 0.05$ , <sup>a</sup>Wilcoxon signed -ranks test, SD: Standard deviation, CI: Confidence Interval. BUN: Blood urea nitrogen HbA1c: Glycated Hemoglobin LDL-C: Low-density lipoprotein cholesterol TC: Total cholesterol HDL-C: High-density lipoprotein cholesterol ALT: Alanine aminotransferase AST: Aspartate transaminase BMI: Body Mass Index MHR: Monocyte HDL-C Ratio PAI: Plasma Atherogenic Index.

### Change in Laboratory Parameters After Empagliflozin Use According to Statin Use

The patient group that did not receive statins before empagliflozin had lower levels of triglyceride (mg/dl) ( $p = 0.017$ ) and PAI ( $p = 0.021$ ). In the group receiving statin, glucose ( $p = 0.039$ ) and HbA1c ( $p = 0.006$ ) levels were higher total cholesterol level ( $p = 0.045$ ) was lower after empagliflozin treatment. Both statin and non-statin patients had decreased glucose, HbA1c, total cholesterol, triglyceride, and PAI levels after empagliflozin use ( $p < 0.001$ ,  $p < 0.01$ , and  $p < 0.05$ , respectively), whereas BUN levels were detected to be increased ( $p < 0.05$ ). Depending on statin use, the mean glucose, HbA1c, total cholesterol, triglyceride, PAI, and BUN levels did not significantly change ( $p > 0.05$ ). The patients not using statins showed a decrease in monocyte count ( $p < 0.001$ ) and MHR ( $p < 0.001$ ) and an increase in sodium ( $p = 0.046$ ) level after empagliflozin. In the patients treated with statins, empagliflozin use led to an increase in HDL-C levels ( $p = 0.05$ ). The decrease in monocyte level after empaglifloz-

in treatment was statistically significantly higher in the patients not on statins compared to those treated with statins ( $p = 0.020$ ) (Table IV).

### Discussion

In our clinical study, we examined metabolic and cardiovascular risk markers MHR and PAI levels in obese and non-obese patients with T2DM. We aimed to investigate the impact of empagliflozin treatment on MHR and PAI values, inflammation markers in cardiovascular disease and diabetes, in T2DM patients. The results of our study presented that empagliflozin treatment significantly lowered MHR and PAI values as well as glucose and HbA1c levels in both obese and non-obese patients.

Over the last three decades, the prevalence of T2DM has doubled, and it is projected to impact approximately half a billion people in the upcoming 30 years<sup>22</sup>. Female gender and advanced age are predisposing factors for T2DM<sup>23</sup>. Of the included patients, 59.8% were female, and 40.2% were male, with an overall mean age of 57.5 years.

**Table III.** Comparison of laboratory parameters before and after empagliflozin use.

Variables	BMI	Empagliflozin			<i>p</i> -value <sup>a</sup>
		Before Mean ± SD	After Mean ± SD	Difference Mean (95% CI)	
Glucose (mg/dL)	< 30	216.20 ± 76.88	175.15 ± 76.77	-41.04 (-67.09; -15.00)	<b>0.003*</b>
	≥ 30	189.40 ± 85.93	148.09 ± 67.44	-41.31 (-61.61; -21.01)	<b>&lt; 0.001*</b>
	<i>p</i> -value <sup>b</sup>	<b>0.014*</b>	<b>0.028*</b>	0.880	
HbA1c (%)	< 30	9.74 ± 1.96	8.28 ± 1.95	-1.46 (-2.06; -0.85)	<b>&lt; 0.001*</b>
	≥ 30	8.49 ± 2.19	7.27 ± 1.58	-1.23 (-1.81; -0.65)	<b>&lt; 0.001*</b>
	<i>p</i> -value <sup>b</sup>	<b>0.004*</b>	<b>0.002*</b>	0.403	
BUN (mg/dl)	< 30	23.42 ± 12.10	30.94 ± 19.91	7.53 (2.33; 12.72)	<b>0.015*</b>
	≥ 30	21.90 ± 17.47	25.44 ± 19.03	3.54 (-0.46; 7.53)	<b>0.031*</b>
	<i>p</i> -value <sup>b</sup>	0.063	0.087	0.280	
Creatinine (mg/dl)	< 30	0.85 ± 0.21	0.88 ± 0.33	0.04 (-0.02; 0.09)	0.290
	≥ 30	0.81 ± 0.21	0.83 ± 0.25	0.02 (-0.02; 0.06)	0.443
	<i>p</i> -value <sup>b</sup>	0.192	0.348	0.803	
Sodium (mEq/L)	< 30	137.95 ± 2.54	138.45 ± 2.26	0.50 (-0.58; 1.58)	0.229
	≥ 30	138.96 ± 2.83	139.45 ± 2.69	0.49 (-0.18; 1.15)	0.219
	<i>p</i> -value <sup>b</sup>	<b>0.046*</b>	<b>0.041*</b>	0.684	
Potassium (mEq/L)	< 30	4.66 ± 0.35	4.55 ± 0.37	-0.11 (-0.22; -0.01)	<b>0.046*</b>
	≥ 30	4.48 ± 0.45	4.53 ± 0.48	0.05 (-0.06; 0.15)	0.394
	<i>p</i> -value <sup>b</sup>	<b>0.035*</b>	0.793	<b>0.045*</b>	
Calcium (mg/dL)	< 30	9.76 ± 0.35	9.63 ± 0.53	-0.12 (-0.30; 0.05)	0.138
	≥ 30	9.60 ± 0.48	9.70 ± 0.42	0.10 (-0.02; 0.22)	0.092
	<i>p</i> -value <sup>b</sup>	0.112	0.657	<b>0.031*</b>	
Hemoglobin (g/dL)	< 30	14.15 ± 1.77	14.14 ± 1.64	-0.01 (-0.39; 0.36)	0.966
	≥ 30	13.66 ± 1.94	14.14 ± 2.53	0.48 (-0.05; 1.00)	0.119
	<i>p</i> -value <sup>b</sup>	0.180	0.500	0.266	
Hematocrit (%)	< 30	42.22 ± 4.66	42.68 ± 4.68	0.46 (-0.58; 1.50)	0.307
	≥ 30	41.31 ± 5.27	41.69 ± 5.86	0.38 (-0.53; 1.29)	0.173
	<i>p</i> -value <sup>b</sup>	0.410	0.513	0.987	
Total Cholesterol (mg/dl)	< 30	206.00 ± 52.08	175.11 ± 39.06	-30.89 (-46.36; -15.42)	<b>&lt; 0.001*</b>
	≥ 30	189.97 ± 52.58	190.65 ± 65.05	0.68 (-12.65; 14.01)	0.139
	<i>p</i> -value <sup>b</sup>	0.155	0.243	<b>0.008*</b>	
LDL-C (mg/dl)	< 30	132.83 ± 41.42	129.33 ± 29.60	-3.50 (-11.90; 4.90)	0.764
	≥ 30	118.62 ± 40.35	122.05 ± 36.02	3.43 (-2.81; 9.67)	0.303
	<i>p</i> -value <sup>b</sup>	0.128	0.207	0.411	
HDL-C (mg/dl)	< 30	44.85 ± 12.72	44.71 ± 11.53	-0.14 (-3.80; 3.52)	0.795
	≥ 30	45.80 ± 11.89	49.05 ± 14.48	3.25 (0.43; 6.08)	0.054
	<i>p</i> -value <sup>b</sup>	0.287	0.113	0.367	
ALT (IU/L)	< 30	24.09 ± 21.25	20.73 ± 11.99	-3.36 (-9.542.82)	0.476
	≥ 30	23.33 ± 14.56	22.31 ± 10.80	-1.02 (-4.041.99)	0.945
	<i>p</i> -value <sup>b</sup>	0.721	0.273	0.363	
AST (IU/L)	< 30	21.53 ± 17.60	18.79 ± 7.09	-2.74 (-7.86; 2.37)	0.650
	≥ 30	22.10 ± 12.07	21.25 ± 10.04	-0.85 (-3.05; 1.35)	0.928
	<i>p</i> -value <sup>b</sup>	0.387	0.227	0.748	
Triglycerides (mg/dl)	< 30	233.65 ± 154.50	171.26 ± 81.77	-62.39 (-106.69; -18.09)	<b>0.001*</b>
	≥ 30	197.37 ± 106.77	173.77 ± 126.58	-23.59 (-43.30; -3.89)	<b>0.007*</b>
	<i>p</i> -value <sup>b</sup>	0.144	0.669	0.104	
Monocytes (10 <sup>3</sup> /mm <sup>3</sup> )	< 30	669.57 ± 168.25	605.65 ± 151.84	-63.91 (-110.38; -17.45)	<b>0.023*</b>
	≥ 30	701.01 ± 158.76	609.49 ± 158.13	-91.52 (-130.20; -52.84)	<b>&lt; 0.001*</b>
	<i>p</i> -value <sup>b</sup>	0.295	0.994	0.130	
MHR	< 30	16.04 ± 4.85	14.15 ± 4.22	-1.89 (-3.43; -0.35)	<b>0.045*</b>
	≥ 30	16.32 ± 7.05	13.55 ± 5.84	-2.77 (-4.20; -1.33)	<b>&lt; 0.001*</b>
	<i>p</i> -value <sup>b</sup>	0.627	0.188	0.219	
PAI	< 30	0.66 ± 0.30	0.55 ± 0.27	-0.12 (-0.19; -0.04)	<b>0.003*</b>
	≥ 30	0.59 ± 0.27	0.51 ± 0.27	-0.09 (-0.14; -0.04)	<b>0.001*</b>
	<i>p</i> -value <sup>b</sup>	0.092	0.323	0.612	

\**p* < 0.05, <sup>a</sup>Wilcoxon signed-ranks test, <sup>b</sup>Mann-Whitney U test, SD: Standard deviation, CI: Confidence Interval. BUN: Blood urea nitrogen HbA1c: Glycated Hemoglobin LDL-C: Low-density lipoprotein cholesterol TC: Total cholesterol HDL-C: High-density lipoprotein cholesterol ALT: Alanine aminotransferase AST: Aspartate transaminase BMI: Body Mass Index MHR: Monocyte HDL-C Ratio PAI: Plasma Atherogenic Index.

**Table IV.** Comparison of pre-empagliflozin and post-empagliflozin laboratory parameters according to statin use.

Variables	Statin	Empagliflozin			p-value <sup>a</sup>
		Before Mean ± SD	After Mean ± SD	Difference Mean (95% CI)	
Glucose (mg/dL)	Yes	205.72 ± 84.33	170.78 ± 76.33	-34.94 (-59.96; -9.92)	<b>0.019</b>
	No	195.11 ± 83.00	149.60 ± 68.02	-45.51 (-66.29; -24.73)	<b>&lt; 0.001*</b>
	<b>p-value<sup>b</sup></b>	0.315	<b>0.039*</b>	0.265	
HbA1c (%)	Yes	9.48 ± 2.08	8.22 ± 1.96	-1.26 (-1.86; -0.65)	<b>&lt; 0.001*</b>
	No	8.67 ± 2.20	7.31 ± 1.59	-1.36 (-1.94; -0.78)	<b>&lt; 0.001*</b>
	<b>p-value<sup>b</sup></b>	0.057	<b>0.006*</b>	0.946	
BUN (mg/dl)	Yes	23.64 ± 14.67	28.77 ± 19.92	5.13 (0.36; 9.90)	<b>0.034</b>
	No	21.65 ± 16.20	26.75 ± 19.25	5.11 (0.81; 9.41)	<b>0.017*</b>
	<b>p-value<sup>b</sup></b>	0.268	0.566	0.981	
Creatinine (mg/dl)	Yes	0.85 ± 0.22	0.88 ± 0.33	0.03 (-0.03; 0.09)	0.356
	No	0.80 ± 0.20	0.82 ± 0.23	0.02 (-0.02; 0.06)	0.368
	<b>p-value<sup>b</sup></b>	0.215	0.236	0.887	
Sodium (mEq/L)	Yes	138.60 ± 3.20	138.73 ± 2.46	0.13 (-0.79; 1.04)	0.715
	No	138.62 ± 2.43	139.37 ± 2.65	0.75 (0.03; 1.47)	<b>0.046*</b>
	<b>p-value<sup>b</sup></b>	0.977	0.136	0.280	
Potassium (mEq/L)	Yes	4.53 ± 0.41	4.54 ± 0.41	0.01 (-0.11; 0.13)	0.785
	No	4.55 ± 0.44	4.53 ± 0.46	-0.02 (-0.13; 0.08)	0.458
	<b>p-value<sup>b</sup></b>	0.639	0.802	0.449	
Calcium (mg/dl)	Yes	9.71 ± 0.33	9.64 ± 0.51	-0.07 (-0.21; 0.08)	0.257
	No	9.62 ± 0.50	9.70 ± 0.42	0.08 (-0.06; 0.23)	0.166
	<b>p-value<sup>b</sup></b>	0.377	0.555	0.067	
Hemoglobin (g/dL)	Yes	13.87 ± 1.73	14.21 ± 1.64	0.34 (-0.07; 0.74)	0.091
	No	13.82 ± 2.01	14.09 ± 2.60	0.27 (-0.28; 0.83)	0.870
	<b>p-value<sup>b</sup></b>	0.884	0.323	0.314	
Hematocrit (%)	Yes	41.73 ± 4.77	42.59 ± 4.44	0.86 (-0.31; 2.04)	0.121
	No	41.59 ± 5.28	41.68 ± 6.09	0.09 (-0.75; 0.93)	0.442
	<b>p-value<sup>b</sup></b>	0.882	0.555	0.323	
Total Cholesterol (mg/dl)	Yes	194.33 ± 56.34	179.41 ± 74.88	-14.92 (-35.65; 5.80)	<b>0.012*</b>
	No	196.90 ± 50.44	188.90 ± 40.57	-8.00 (-18.49; 2.49)	<b>0.017*</b>
	<b>p-value<sup>b</sup></b>	0.639	<b>0.045*</b>	0.588	
LDL-C (mg/dl)	Yes	120.76 ± 44.32	117.94 ± 32.75	-2.82 (-10.64; 4.99)	0.832
	No	125.97 ± 39.01	129.41 ± 34.04	3.43 (-3.11; 9.97)	0.483
	<b>p-value<sup>b</sup></b>	0.407	0.087	0.706	
HDL-C (mg/dl)	Yes	44.12 ± 11.30	46.38 ± 12.23	2.27 (-1.33; 5.86)	<b>0.035</b>
	No	46.36 ± 12.71	48.19 ± 14.47	1.82 (-1.07; 4.72)	0.388
	<b>p-value<sup>b</sup></b>	0.201	0.584	0.346	
ALT (IU/L)	Yes	22.38 ± 10.74	21.46 ± 9.79	-0.92 (-3.91; 2.07)	0.398
	No	24.45 ± 20.56	21.92 ± 12.18	-2.53 (-7.05; 1.99)	0.923
	<b>p-value<sup>b</sup></b>	0.324	0.847	0.295	
AST (IU/L)	Yes	20.53 ± 8.61	20.06 ± 7.84	-0.47 (-1.86; 0.93)	0.607
	No	22.85 ± 17.12	20.57 ± 9.99	-2.28 (-6.07; 1.51)	0.891
	<b>p-value<sup>b</sup></b>	0.707	0.927	0.752	
Triglycerides (mg/dl)	Yes	247.37 ± 163.47	197.24 ± 158.90	-50.14 (-94.58; -5.69)	<b>0.003*</b>
	No	185.46 ± 86.77	156.04 ± 57.00	-29.42 (-46.29; -12.55)	<b>0.002*</b>
	<b>p-value<sup>b</sup></b>	<b>0.017*</b>	0.290	0.432	
Monocytes (10 <sup>3</sup> /mm <sup>3</sup> )	Yes	676.86 ± 173.33	635.10 ± 164.38	-41.76 (-90.31; 6.78)	0.059
	No	698.11 ± 154.95	589.46 ± 146.86	-108.65 (-145.28; -72.02)	<b>&lt; 0.001*</b>
	<b>p-value<sup>b</sup></b>	0.380	0.150	<b>0.020*</b>	
MHR	Yes	16.13 ± 5.92	14.73 ± 5.90	-1.40 (-2.83; 0.03)	0.065
	No	16.27 ± 6.60	13.11 ± 4.76	-3.16 (-4.66; -1.67)	<b>&lt; 0.001*</b>
	<b>p-value<sup>b</sup></b>	0.675	0.147	0.104	
PAI	Yes	0.70 ± 0.28	0.56 ± 0.29	-0.13 (-0.20; -0.07)	<b>&lt; 0.001*</b>
	No	0.57 ± 0.27	0.49 ± 0.25	-0.07 (-0.12; -0.02)	<b>0.005*</b>
	<b>p-value<sup>b</sup></b>	<b>0.021*</b>	0.310	0.252	

\**p* < 0.05, <sup>a</sup>Wilcoxon signed-ranks test, <sup>b</sup>Mann-Whitney U test, SD: Standard deviation, CI: Confidence Interval. BUN: Blood urea nitrogen HbA1c: Glycated Hemoglobin LDL-C: Low-density lipoprotein cholesterol TC: Total cholesterol HDL-C: High-density lipoprotein cholesterol ALT: Alanine aminotransferase AST: Aspartate transaminase BMI: Body Mass Index MHR: Monocyte HDL-C Ratio PAI: Plasma Atherogenic Index.

Empagliflozin is one of three approved SGLT2 inhibitors<sup>23</sup>. In a study by Rosenstock et al<sup>24</sup>, a statistically significant decrease was reported in HbA1c, fasting plasma glucose, and body weight after 12 weeks of empagliflozin treatment. In our study, similar to the literature, a significant reduction was detected in fasting plasma glucose and HbA1c levels of the patients after a mean duration of 30.7 weeks of empagliflozin treatment ( $p < 0.001$ ). Unexpectedly, after empagliflozin treatment, the non-obese patients had higher HbA1c and fasting glucose levels than the obese patients. There could be two reasons for this. Firstly, SGLT2 inhibitors are only given to patients in Turkey if their HbA1c level is above 7% after using the highest possible dose of metformin. Secondly, non-obese patients may struggle more with sticking to their diet and may have fewer hospital visits. In addition, this finding also implies that the non-obese patient group had a higher severity of diabetes, underscoring the increased significance of the obtained results.

SGLT2 inhibitors are linked to a slight rise in HDL-C along with an increase in LDL-C, while simultaneously lowering triglyceride levels<sup>25-27</sup>. A meta-analysis<sup>28</sup> including 34 randomized controlled trials indicated that the treatment with SGLT2 inhibitors elevated HDL-C (mean difference 1.93 mg/dL), LDL-C (mean difference 3.5 mg/dL) and reduced serum triglycerides (mean difference 7.8 mg/dL). In the comparative study between empagliflozin and placebo, small elevations in HDL and LDL cholesterol and a small reduction in triglyceride levels were determined in the empagliflozin group<sup>28</sup>. In our results, the increase in HDL-C and a decrease in LDL-C were statistically significant, while the decrease in total cholesterol level was not significant, in both obese and non-obese groups after empagliflozin treatment. Notably, triglyceride levels significantly decreased in both groups.

The potential role of statins as antiatherosclerotic and antithrombotic drugs, in addition to their lipid-reducing action, has been examined in the literature<sup>29</sup>. These compounds may induce relevant vascular protective mechanisms by suppressing platelet activity and monocyte tissue factor expression. Statins reduce inflammatory agents such as CRP, thromboxan A2, and TNF- $\alpha$ <sup>30</sup>. Our results indicated that empagliflozin treatment significantly increased HDL-C levels in the patient group receiving statin. There was a slight yet statistically not significant reduction in LDL-C in the statin-receiving patients compared

to the non-statin patients. Notably, a significant decrease in triglyceride levels was observed in both statin and no-statin-using groups. On the other hand, the initial triglyceride levels were higher in the patients who used statins before empagliflozin treatment.

Although there was a minimal increase in hemoglobin and hematocrit values after empagliflozin treatment in our patients, this increase did not attain statistical significance. In the study of List et al<sup>31</sup>, a significant hematocrit elevation was found after 12 weeks of dapagliflozin use. Yoshimoto et al<sup>32</sup> indicated that dapagliflozin did not change the creatinine level but caused an increase in the BUN level. In our study, a significant increase in hemoglobin and hematocrit in both obese and non-obese patient groups following empagliflozin treatment was accompanied by high BUN levels. This suggests that this effect of empagliflozin may be attributed to hemoconcentration due to its diuretic effect. Empagliflozin treatment led to a significant decrease in the monocyte count of the patients in both groups. The reduction in the monocyte count with the use of empagliflozin treatment was significantly higher in the patients not using statin compared to those using statin. This may be an undetermined effect of prolonged empagliflozin use.

In low-severity inflammation, monocytes are activated, some of which turn into lipid-laden macrophages<sup>33</sup>. Thus, monocytes and macrophages trigger the formation or progression of cardiovascular diseases. Johnsen et al<sup>34</sup> reported that monocyte increase was a predictor of plaque development in previously non-plaque arteries. There are many recent studies indicating that HDL has an effect on monocyte activation and inflammation in the occurrence of atherosclerosis<sup>35,36</sup>. Moreover, it has been reported that HDL has an effect on the endothelium by elevating nitric oxide production and exhibits anti-inflammatory properties. Monocyte and HDL parameters can be considered as an indirect indicator of inflammation<sup>37</sup>. The plasma atherogenic index is a recently introduced index that effectively reflects cardiovascular disease and dyslipidemia risk<sup>38</sup>. PAI, which is basically calculated by the logarithmic ratio of TG to HDL, has been shown to be a powerful predictor of major cardiovascular diseases that can lead to death such as coronary artery disease and acute coronary syndrome<sup>39-41</sup>. In addition, the relationship between obesity and PAI has been demonstrated to be strong<sup>41</sup>. MHR and PAI values are used as cardiac biomarkers in diabetic patients<sup>39-41</sup>. There are stud-

ies showing the anti-inflammatory and antioxidant properties of empagliflozin treatment in T2DM patients<sup>42,43</sup>. However, we could not find any study in the literature investigating the effect of empagliflozin treatment on MHR and PAI levels. Chronic inflammatory disorders and dyslipidemia are important contributors to the development of atherosclerotic cardiovascular disease in individuals with T2DM. High PAI and MHR values are associated with cardiovascular disease<sup>36-41</sup>. Cardiovascular mortality is the major cause of death in T2DM patients. The recently published Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study revealed that empagliflozin decreased the primary major adverse cardiac event endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) by 14% in T2DM patients with high cardiovascular disease risk<sup>44</sup>. Up to 50% of diabetes patients suffer from microvascular complications, including diabetic peripheral neuropathy, diabetic retinopathy and diabetic nephropathy<sup>45,46</sup>. There also exists evidence suggesting that inflammation may play a crucial role in the occurrence of microvascular complications. In addition, oxidative stress strongly influences the pathogenesis of diabetic complications<sup>47</sup>. In the study by Eid et al<sup>48</sup> in which the effect of empagliflozin on diabetic microvascular complications was investigated, it was reported that the effect empagliflozin was not significant on neuropathy in T2DM patients. Mehta et al<sup>49</sup> reported that there was no difference between empagliflozin and other oral antihyperglycemic drugs in the improvement of diabetic neuropathy. The MHR and PAI have been shown to be good predictors of diabetes mellitus. These are simple, fast and useful laboratory indexes that can be calculated from hemogram parameters and lipid counts that are commonly used in routine practice. In our study, a significant decrease was found in MHR and PAI values after empagliflozin treatment in the obese and non-obese diabetic patients. Changes in monocyte counts and HDL in both groups, regardless of statin use, can be attributed to the use of empagliflozin. Nagareddy et al<sup>50</sup> showed in T1DM mouse models that the use of SGLT2 inhibitors to lower blood glucose levels prevented monocytosis induced by diabetes. This, in turn, decreased the attachment of monocytes to the artery wall and consequently improved lesion regression in diabetic mice<sup>50</sup>. Furthermore, a study put forward that rather than glucose directly influencing the bone marrow hematopoietic progenitor cell compartment, myelopoiesis was stimulated by

neutrophil-derived S100A8/S100A9 through the activation of the receptor for advanced glycation end products (RAGE) on bone marrow progenitor cells<sup>50</sup>. SGLT2 inhibitors exhibit a significant beneficial influence on cardiac failure and advancement of renal disease, whereas their impact on reducing atherosclerotic CVD is relatively modest. These inhibitors are primarily effective in patients who already have established atherosclerotic disease<sup>51</sup>. Suggested beneficial mechanisms that are not primarily linked to blood glucose-lowering effects are natriuresis and osmotic diuresis, decreased inflammation, oxidative stress, arterial stiffness, decrease in blood pressure and body weight, and renoprotective effects<sup>52,53</sup>. Based on their safety profiles, it appears that SGLT2 inhibitors do not lower monocyte counts in individuals with T2DM, suggesting that the impact of SGLT2 inhibitors on monocytosis seen in diabetic mice may not necessarily apply to humans. The results of our study regarding the increase in HDL with empagliflozin treatment are consistent with the literature; however, more research is essential to elucidate the variation in monocyte counts in patients with diabetes.

### **Limitations**

The major limitation of our study is the fact that it was conducted retrospectively. Due to its retrospective nature, it is not known that the patients took antidiabetic drugs regularly before starting empagliflozin treatment. Another limitation is whether their drug use was regular after empagliflozin initiation.

### **Conclusions**

In our study, a significant decrease was found in MHR and PAI levels in both obese and non-obese diabetic patients after empagliflozin use. Accordingly, MHR and PAI can be proposed to be used as cardiac inflammation markers in patients using empagliflozin. The fact that empagliflozin decreases MHR and PAI levels in obese and non-obese T2DM patients indicates that it provides anti-inflammatory activity in these patients.

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### **Conflict of Interest**

The Authors declare that they have no conflict of interest.

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### Ethics Approval

Our study was approved by the Non-interventional Clinical Researchs Ethics Committee of the Faculty of Medicine, University of Gaziosmanpaşa (approval decision number: 2022-KAEK-183, Date: 08.09.2022).

### Informed Consent

An informed consent form was obtained from the participants before participating in the study.

### Availability of Data and Materials

The authors give their consent for the article publication.

### Authors' Contributions

Hakan Sivgin: conception, design of the study, and supervision; Sirin Çetin: analysis and interpretation of data; All authors: drafting the article and making critical revisions related to the relevant intellectual content of the manuscript. All authors approved the final version of the article to be published.

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