LOKMAN HEKIM HEALTH SCIENCES

DOI: 10.14744/lhhs.2021.80001
Lokman Hekim Health Sci 2021;1(3):74–80

lokmanhekimhs.com

ORIGINAL ARTICLE

Effects of Empagliflozin on Carotid Intima-Media Thickness and Epicardial Fat Tissue Volume in Patients with Type-2 Diabetes Mellitus

Empagliflozin Tip 2 Diabetes Mellituslu Hastalarda Karotis İntima-Media Kalınlığını ve Epikardiyal Yağ Doku Hacmini Geriletebilir

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Abstract

Introduction: Changes in epicardial adipose tissue (EAT) and carotid intima-media thickness (CIMT), which are markers of subclinical atherosclerosis, were investigated in patients with type-2 diabetes mellitus (DM) initiated with empagliflozin.

Methods: Thirty-seven patients with type-2 DM were included in this study. Empagliflozin was administered to all patients within the indication, and EAT and CIMT measurements were performed. After an average of 6 months of treatment, the effects of empagliflozin on EAT and CIMT were evaluated through remeasurements.

Results: The mean age of the study group was 56.95±11.61 years, and 56.8% (n=21) of the participants were women. The mean duration of DM was 8.6±3.3 years. Significant reductions were found in weight, waist circumference, body mass index, and systolic and diastolic blood pressure at the treatment initiation and post-treatment evaluation ($p<0.001$ for each). Significant reductions in EAT and CIMT were noted with empagliflozin treatment (7.6±1.7 vs. 6.7±1.3, $p<0.001$ and 9.0±2.2 vs. 7.7±1.4, $p=0.001$, respectively).

Discussion and Conclusion: Treatment with empagliflozin may improve systemic metabolic parameters and decrease the EAT volume and CIMT in patients with type-2 DM. This could result in a reduced risk of cardiovascular events.

Keywords: Empagliflozin; Epicardial adipose tissue; Carotid intima-media thickness; Type-2 diabetes mellitus

Cite this article as: *Ardahanlı İ, Aslan R, Çelik M, Akgün O, Akyüz O. Effects of Empagliflozin on Carotid Intima-Media Thickness and Epicardial Fat Tissue Volume in Patients with Type-2 Diabetes Mellitus. Lokman Hekim Health Sci 2021;1(3):74–80.*

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Diabetes mellitus (DM) is an important global public health problem, and its incidence has increased during the last 30 years. It is an important cause of mortality and morbidity due to the complications it causes. These complications include conditions such as coronary heart disease, stroke, and peripheral artery disease. The regression of atherosclerotic plaques and the reduction of plaque load have lowered plasma cholesterol levels.[1] Whether plaque development in diabetic patients is due to hyperinsulinemia, erroneous insulin signal, or hyperlipidemia, is still a matter of debate. Empagliflozin, one of the sodium-glucose cotransporter-2 (SGLT2) inhibitors, has recently been shown as beneficial in cardiovascular mortality in diabetic patients, especially those with heart failure and diastolic dysfunction.[2] SGLT2 inhibitors exert their effects on the brushy border membrane in the proximal convoluted tubules epithelium of the kidney. Inhibition of SGLT2 prevents glucose reuptake from the glomerular filtrate, lowers blood glucose levels, and stimulates urinary glucose excretion. Although the pharmacology of SGLT2 inhibition is well understood, mechanisms for its cardiovascular benefits are still under investigation. One proposed mechanism is the beneficial effect of glucose reduction on inflammatory processes in atherosclerosis.

The first clinical signs of cardiovascular disease usually occur in the advanced stages of atherosclerosis. However, there is a long silent period in which there are no clinical symptoms; arterial wall changes develop in this period and begin with diffuse intimal thickening. Carotid intima-media thickness (CIMT) is a parameter that can be used as an early indicator of atherosclerosis and can be measured by non-invasive methods.[3–5] Epicardial adipose tissue (EAT) is a specialized visceral adipose tissue located on the heart's surface. While physiologically providing mechanical protection, it helps to meet the myocardium's energy needs and plays a cardioprotective role by producing anti-inflammatory adipokines and cytokines. However, the situations in which EAT increases may be associated with pathology. EAT increase is known to be a risk factor for atherosclerosis, visceral obesity, and metabolic syndrome.[5] EAT measurement is a practical tool used to obtain information about the cardiovascular status of a subject. It is possible to easily evaluate a non-invasive, inexpensive, and reproducible imaging method such as the transthoracic echocardiography.

Our study aimed to investigate the changes in of EAT and CIMT in patients with type-2 DM by adding empagliflozin to the standard treatment.

Materials and Methods

Study Population

The study, which was planned as a single-center study, included 77 patients who applied to the endocrinology outpatient clinic between May 2020 and July 2020 and were diagnosed with type-2 DM. Patients with known coronary artery disease, heart failure (left ventricular ejection fraction <50%), severe valvular heart disease, or cardiomyopathy; patients with a previous history of cardiac surgery for any reason, renal failure (glomerular filtration rate <15 mL/min); patients with hepatic impairment (serum transaminase levels greater than twice the upper limit of normal); patients with the previous stroke, transient ischemic attack, malignancy diagnosis; patients with active infection; those who did not complete the treatment; and those who were not followed up were not included in the study.

Assessment and Measurements

Medical history was taken from all participants, and a complete physical examination was performed. The current medications the patients took were checked. Height, weight, and waist circumference were measured, and body mass index (BMI) was calculated using the following formula: BMI=weight (kg)/height (meters) 2. The obtained data were recorded. A signed consent form was obtained from all participants in the study group. The study was designed following the Helsinki Declaration and received approval from the local Ethics Committee.

Participants were divided into two groups before the initiation of empagliflozin and after six months of treatment. The patients were started at 10 mg as an initial dose, and then, the dose was increased to 25 mg when necessary according to their follow-up. All anthropometric measurements, biochemical analyses, and EAT and CIMT measurements were measured and recorded before starting treatment and after 6 months of treatment.

Complete blood count and biochemical analyzes were performed from all participants in the study following 12 hours of fasting. In biochemical analysis, fasting blood glucose, HbA1c, insulin levels, lipid profiles, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, creatinine, sodium, potassium, and thyroid-stimulating hormone levels were measured. All laboratory analyzes were performed by a laboratory technician who was blinded to patient data.

Echocardiographic and Ultrasonographic Evaluation

Echocardiographic evaluation was performed in the Cardiology Department's echocardiography laboratory with a Philips (Epiq 7, Holland) brand device. All measurements were performed in five consecutive cardiac cycles in the left lateral decubitus position, accompanied by electrocardiography (ECG) following recommendations by the American Echocardiography Society, and the averages of these measurements were used for statistical analysis. The EAT was accepted as the hypoechogenic area between the visceral pericardium and right ventricular free wall. EAT was obtained by measuring the space between the right ventricle and visceral pericardium on the line drawn perpendicular to the right ventricle midventricular free wall at the end of the systole in the parasternal long-axis view (Fig. 1). Systole and diastole differentiation was made using ECG, and measurements were repeated during three to four cardiac cycles. All measurements were made with the help of cardiologists who were blinded to patient data.

The left common carotid artery was examined while the patients were in the supine position. It was ensured that the near and distant walls of the artery were viewed parallel to each other. The distal posterior wall, 10 mm from the carotid bifurcation, was targeted. Images were frozen and enlarged when the image was obtained. The arteries' near and distant walls were parallel to each other, and the media-adventitia borders were double lines. Intima-media thickness was measured from four different points with 1 mm distances at the end of the diastole, the R wave of the ECG recording, and averaged.[6] The measurement of CIMT is presented in Figure 2.

Statistical Analysis

The SPSS 23.0 package computer program (SPSS, Inc., Chicago, IL) was used for the statistical data evaluation. According to their distribution, continuous variables were expressed as mean±standard deviation, while categorical variables were shown as frequency and percentage (%). The data distribution was evaluated using the Kolmogorov–Smirnov test. Comparison between groups was carried out using the Mann–Whitney U or t-test according to the distribution of data. Chi-squared test was used to evaluate categorical variables between groups. A p-value of <0.05 was considered significant in the statistical analysis obtained.

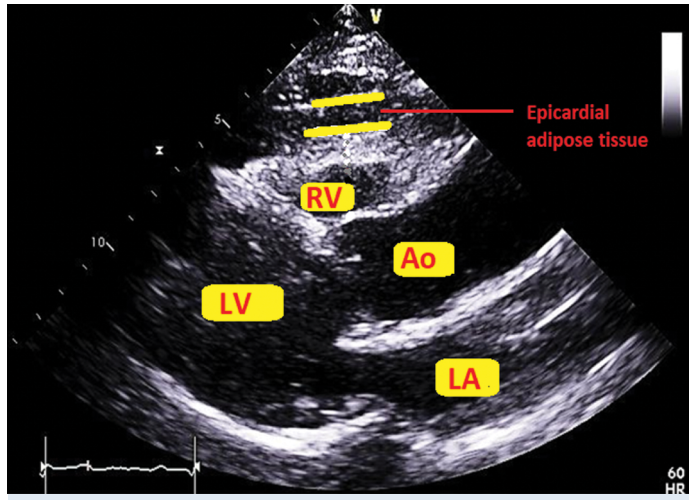

Figure 1. Epicardial adipose tissue in parasternal long-axis imaging.

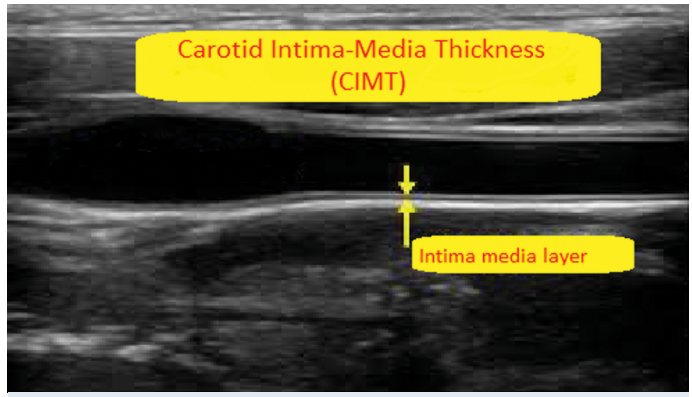

Figure 2. CIMT measurement.

Results

Thirty-seven patients with type-2 DM were included in the study. They were compared when empagliflozin was initiated and at the 6-month follow-up. The mean age of the study group was 56.95±11.61 years (age range, 33–74 years), and 56.8% (n=21) of the participants were female. The mean duration of diabetes was 8.6±3.3 years. There were statistically significant reductions in weight, waist circumference, BMI, systolic blood pressure, and diastolic blood pressure at the initiation of treatment and post-treatment evaluation (p<0.001 for each). The comparison of demographic and clinical data is shown in Table 1.

In evaluating biochemical data, a statistically significant decrease in HbA1c was observed with treatment (8.3±2.3% vs. 7.1±1.5%, p=0.034). In contrast, the decrease in fasting plasma glucose levels was not significant (173.8±31.8 mg/dl vs. 145.3±25.5 mg/dl, p=0.327). There was a statistically significant decrease in uric acid level with treatment (5.7±2.7 mg/dl vs. 5.3±1.8 mg/dl,

Table 1. Demographic and clinical data of patients before and after empagliflozin treatment

Parameters	Before treatment (Mean±SD)	After treatment (Mean±SD)	p
Mean age (years)		56.95±11.61	
Sex, male/female (%)		16 (43.2) /21 (56.8%)	
Duration of DM (years)	8.6±3.3		
Weight (kg)	80.0±11.5	77.4±8.6	<**0.001**
Waist circumference (cm)	105.9±14.6	102.4±11.7	<**0.001**
BMI (kg/m^2)	28.9±3.6	28.0±2.6	<**0.001**
SBP (mmHg)	131.7±6.9	127.8±5.3	<**0.001**
DBP (mmHg)	86.2±4.4	83.4±3.8	<**0.001**

SD: Standard deviation; DM: Diabetes mellitus; BMI: Body mass index; SPB: Systolic blood pressure; DBP: Diastolic blood pressure.

p<0.001). Furthermore, there were no significant changes in other biochemical analyzes. In EFT and CIMT measurements, there were significant decreases in both parameters with treatment (7.6±1.7 mm vs 6.7±1.3 mm, p<0.001; and 9.0±2.2 mm vs 7.7±1.4 mm, p=0.001, respectively). The comparison of laboratory values, CIMT, and EAT measurements are presented in Table 2.

Changes in the patients' initial clinical and laboratory values after empagliflozin treatment are presented in Table 3.

Table 2. The comparison of laboratory values, CIMT and EAT measurements

Parameters	Before treatment (Mean±SD)	After treatment (Mean±SD)	p
EAT (mm)	7.6±1.7	6.7±1.3	<**0.001**
CIMT (mm)	9.0±2.2	7.7±1.4	**0.001**
FPG (mg/dL)	173.8±31.8	145.3±25.5	0.327
HbA1c (%)	8.3±2.3	7.1±1.5	**0.034**
Total CHL (mg/dL)	217.4±39.3	206.4±32.0	0.768
HDL-C (mg/dL)	43.5±6.0	45.5±5.5	0.848
LDL-C (mg/dL)	138.4±39.5	130.2±33.1	0.435
Triglyceride (mg/dL)	177.4±71.5	153.7±19.9	0.991
AST, IU/L	34.7±10.6	29.8±12.0	0.942
ALT, IU/L	30.2±11.4	27.0±11.1	0.208
Na (mEq/L)	139.4±5.1	137.8±4.6	0.538
K (mEq/L)	4.6±0.6	4.7±0.5	0.878
Uric acid (mg/dL)	5.7±2.7	5.3±1.8	**0.001**

SD: Standard deviation; EAT: Epicardial adipose tissue; CIMT: Carotid intima-media thickness; FBG: Fasting plasma glucose; CHL: Cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanin aminotransferase; Na: Sodium; K: Potassium.

Discussion

When the relationship between EAT and CIMT and empagliflozin, an SGLT-2 inhibitor, was investigated in patients with type-2 DM, it was found that there was a significant regression between EAT and CIMT with the use of empagliflozin for 6 months.

DM affects all vascular structures in the body and is usually a systematic disease that progresses asymptomatically until it causes clinical end-organ damage. This characteristic causes a delay in the diagnosis of vascular complications. Therefore, early detection of vascular damage is vital in the subclinical period in DM. This allows us to take the necessary precautions and may positively affect the prognosis of DM's atherosclerotic complications in the long term. For this purpose, it has been shown in previous studies that EAT and CIMT can be used as a predictive indicator of cardiovascular risk.[3–5]

Transthoracic ECG, which is a non-invasive, inexpensive, and reproducible method, is used to measure EAT, which is a visceral adipose tissue with paracrine effects and vasogenic and inflammatory effects in the vicinity of the visceral pericardium. Furthermore, it is now known that EAT is associated with coronary artery disease.[4,7] CIMT is another subclinical finding of atherosclerosis with proven association with atherosclerotic coronary artery disease.[8] It is known that EAT and CIMT increase in echocardiography in patients with long-term uncontrolled DM.[9,10]

The benefits of empagliflozin, an SGLT2 inhibitor, and which has recently become preferred for its positive cardiac effects in DM treatment, in heart failure and diastolic dysfunction, has been demonstrated in the EMPA-REG OUTCOME trial.[11] However, there are not enough studies on humans showing its effects on the atherosclerotic process. The results of this study are significant in this respect.

Previous experimental studies have shown that in diabetic mice applied empagliflozin, the plaques in the aortic root regressed at autopsy significantly. The proliferation of macrophages located in the plaques and leukocytes' adhesion to the vascular wall significantly decreased.[12] In the

Table 3. Changes in baseline clinical and laboratory values of patients after empagliflozin therapy

	Change from baseline treatment, Mean	SD	Std. Error, Mean	95% CI difference		p
				Lower	Upper	
Δ Weight (kg)	-2.56	7.24	1.19	-5.01	-0.18	**0.036**
Δ Waist circumference (cm)	-3.43	7.13	1.17	-5.81	-1.06	**0.006**
Δ BMI (kg/m^2)	-0.92	2.50	0.41	-1.76	-0.09	**0.031**
Δ SBP (mmHg)	-3.91	3.41	0.56	-5.06	-2.78	<**0.001**
Δ DBP (mmHg)	-2.73	2.37	0.39	-3.51	-1.94	<**0.001**
Δ EAT (mm)	-0.89	1.33	0.22	-1.34	-0.45	<**0.001**
Δ CIMT (mm)	-1.29	1.84	0.30	-1.91	-0.69	<**0.001**
Δ FPG (mg/dl)	-28.00	37.36	6.14	-40.46	-15.55	<**0.001**
Δ HbA1c (%)	-1.19	2.23	0.37	-1.94	-0.45	**0.002**
Δ Total CHL (mg/dL)	-11.00	49.46	8.13	-27.49	5.49	0.185
Δ HDL-C (mg/dL)	2.00	8.28	1.36	-0.77	4.76	0.150
Δ LDL-C (mg/dL)	-8.25	48.05	7.90	-24.28	7.77	0.303
Δ Triglyceride (mg/dL)	-23.73	74.27	12.21	-48.49	1.03	0.060
Δ AST (IU/L)	-4.89	15.94	2.62	-10.21	0.42	0.070
Δ ALT (IU/L)	-3.19	17.54	2.89	-9.03	2.66	0.276
Δ Creatinine (mg/dl)	-0.007	0.23	0.04	-0.09	0.069	0.862
Δ Na (mEq/L)	-1.56	6.46	1.06	-3.75	0.56	0.142
Δ K (mEq/L)	0.149	0.76	0.12	-0.10	0.40	0.239
Δ Uric acid (mg/dL)	-0.37	2.35	0.39	-1.16	0.41	0.337

SD: Standard deviation; CI: Confidence interval; SBP; Systolic blood pressure; DBP: Diastolic blood pressure; EAT: Epicardial adipose tissue; CIMT: Carotid intima-media thickness; FBG: Fasting plasma glucose; CHL: Cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanin aminotransferase; Na: Sodium; K: Potassium.

histomorphometric and immunohistochemical analysis of the aortic root of mice in the animal experiment by Dimitriadis et al., it was reported that empagliflozin decreased the expression of the inflammatory molecule VCAM-1, reducing the progression of atherosclerosis, hyperglycemia, and inflammatory process.[13] Again, in a recent experimental study, it was reported that myocardial oxidative stress and fibrosis in the heart of diabetic mice treated with empagliflozin for 8 weeks decreased. In this context, positive outcomes are possible when empagliflozin is an agent that can prevent diabetic cardiomyopathy.[14] Park S.H. et al.[15] recently reported that empagliflozin treatment improved endothelial dysfunction in mice. From all these experimental animal studies, it can be concluded that empagliflozin treatment has additional cardiovascular benefits while lowering blood glucose levels. Furthermore, Irace et al. reported that empagliflozin significantly decreased the wall shear stress and intimal thickness in 35 patients with type-2 DM compared to those receiving incretin-based therapy.[16] What made us different from this study was a relatively higher number of patients, longer follow-up time, and simultaneous EAT evaluation.

In a study that evaluated 28 patients with drug-eluting stent implantation, it was reported that the neointimal hyperplasia decreased and the lumen range of the coronary was wider after 1 year with the addition of empagliflozin to the standard therapy.[17] In this study, patients were evaluated by optical coherence tomography. Our study used EAT and CIMT, which are measured with non-invasive, comfortable, and reproducible methods. Another difference noted in our study was the shorter follow-up period for patients, which was 6 months.

It is known that EAT is a good indicator of endothelial dysfunction in diseases such as metabolic syndrome, hyperlipidemia, hypertension, and diabetes.[3–5] Secretion of adipokine with anti-atherogenic and anti-inflammatory activity is among the EAT physiological functions when it is in moderate amount. The best known of these is adiponectin with its antiatherosclerotic properties. However, EAT becomes dysfunctional as its amount increases. As a result, the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha, monocyte chemoattractant protein-1 (MCP-1), nterleukin-1 beta (IL-1 beta), and IL-6 increases, and the release of antiatherosclerotic adiponectin decreases.[18]

To the best of our knowledge, there were no prior studies in the literature regarding the EAT changes in patients given empagliflozin. However, studies investigating the effect of other SGLT-2 inhibitors on EAT are available in the literature. It was thought that dapagliflozin, luseogliflozin, and canagliflozin reduce EAT and may have an effect on preventing cardiovascular events.[19–21] In our study, we found that empagliflozin significantly decreased EAT, similarly to other SGLT-2 inhibitors. We think that the inflammatory effect of EAT is inhibited by empagliflozin. Some previous studies showed that empagliflozin has glucose-lowering properties and anti-inflammatory effects.[22] Another recent study showed that 6 months of empagliflozin treatment did not significantly improve left ventricular (LV) structure, adiposity, and diffuse fibrosis in patients with type-2 DM. Furthermore, this study stated that the beneficial effects of empagliflozin treatment were evident in patients with worse LV substrate and structure. In these studies, cardiac MRI was used to evaluate LV and pericardial adipose tissue in patients.[23] One reason for the study results may be that the imaging methods used in follow-up were different. Other reasons are that age and accompanying comorbid conditions may be different from our study group.

This study has some limitations. First, it was a single-center study, and the number of patients was relatively small. Another limitation was its relatively short duration. Therefore, we could not analyze the long-term effects of empagliflozin. Finally, we could not exclude drugs that could affect glucose metabolism during follow-up. Large, randomized, and clinical cohort studies with more extended observation periods are thus required to evaluate our findings more clearly.

Conclusion

This study showed that there are significant changes in CIMT and EAT, which are subclinical indicators of atherosclerosis, with empagliflozin treatment for 6 months in patients with type-2 DM. It suggests that empagliflozin, which has been proven to reduce mortality and decrease the risk of hospitalization in heart failure, may benefit from its positive effects in the atherosclerotic process in type-2 DM patients and may affect preventing cardiovascular events in these patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: İA, RA, MÇ, OnA, OkA; Design: İA, RA, MÇ, OnA, OkA; Supervision: İA, RA, MÇ, OnA, OkA; Fundings: İA, RA, MÇ; Materials: İA, RA; Data Collection or Processing: İA, RA; Analysis or Interpretation: İA, MÇ; Literature Search: İA, RA, MÇ, OnA, OkA; Writing: İA; Critical Review: İA, MÇ, OnA, OkA.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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