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The effect of empagliflozin on monocyte high-density lipoprotein ratio in patients with type 2 diabetes mellitus

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ABSTRACT

Aim: We aimed to investigate the effect of empagliflozin, which is started in patients with type 2 diabetes mellitus (T2DM), on neutrophil leumphocyte ratio (NLR) and monocyte high-density lipoprotein ratio (MHR), which are used as inflammation, glycemic control and oxidative markers.

Material and Method: The file systems of T2DM patients who used empagliflozin for at least 12 weeks were retrospectively analyzed. Demographic data of the patients were recorded. biochemical and hemogram parameters were compared before and after empagliflozin.

Results: 194 patients were included in the study. Plasma fasting glucose ($p<0.001$), hemoglobin A1c (HbA1c)($p<0.001$), low-density lipoprotein cholesterol (LDL-C) ($p=0.041$), NLR($p=0.002$) and MHR($p=0.042$) values of T2DM patients after empagliflozin treatment were statistically significantly decreased compared to pre-treatment with empagliflozin. HDL-C value($p=0.003$), on the other hand, increased significantly after empagliflozin

Conclusion: NLR and MHR are inexpensive and practical markers of inflammation. This result shows us that NLR and MHR should be used as inflammation markers in patients using empagliflozin.

Keywords: Empagliflozin, MHR, NLR

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease with a complex pathophysiology. Increasing insulin resistance, progressive deterioration of β-cell function, dysfunctional adipocytes, gastrointestinal incretin defects, increased glucose reabsorption from the kidneys, hyperglucagonemia, and neurotransmitter dysfunction may contribute to development of diabetesGlucose control is a central focus in the management of T2DM, and reducing hyperglycemia has been shown to decrease microvascular complications of diabetes (1). Chronic inflammation plays an important role in the pathogenesis of diabetes, its development and complications (2,3). Studies show that the levels of inflammatory cytokines such as CRP, IL-1, IL-6, TNF-α increase in patients with diabetes (4). Neutrophil/lymphocyte ratio (NLR) is an indicator of systemic inflammation and is accepted as a marker of inflammation in complications such as microvascular and macrovascular in diabetic patients (5). The monocyte-to-high density lipoprotein ratio (MHR) has recently been implemented as an indicator of inflammation and oxidative stress. MHR indicates inflammation and oxidative stress due to the proinflammatory effect of the monocytes, as well as the anti-inflammatory and antioxidant effect of the high-density lipoprotein cholesterol (HDL-C). Several studies have used these metrics to determine whether inflammation and atherosclerosis contribute to the etiopathogenesis of cardiovascular and cerebrovascular diseases. MHR has been found to be significant as a biomarker in the development of microvascular complications in diabetic patients (6,7). Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, is a newly developed oral antidiabetic drug to enhance renal glucose excretion or glycosuria and reduce hyperglycaemia in an insulin-independent manner by highly selective inhibition of SGLT2. SGLT2 is mainly located in the apical brush border membrane of the S1 segment of the proximal convoluted tubules, which regulates 90% of the reabsorption of glucose from glomerular filtrate. Therefore, SGLT2 inhibitor can increase the urinary glucose level and reduce blood glucose. Empagliflozin is different form conventional antidiabetic drugs, which

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rely on insulin secretion, and represents a novel class of antidiabetic drugs. It has been approved for the treatment of type 2 diabetes in adults since 2014 (8,9). In our study, we aimed to investigate the effect of empagliflozin, which is started in patients with Type 2DM, on NLR and MHR, which are used as inflammation, glycemic control and oxidative markers.

MATERIAL AND METHOD

This study was planned retrospectively. The study was carried out with the permission of Hitit University Medical Faculty Non-interventional Clinical Researches Ethics Committee (Date: 29.12.2021, Decision No: 2021-88). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who applied to our internal medicine outpatient clinic between 01.01.2019 and 01.01.2022 with a diagnosis of T2DM, who were started on empagliflozin 10 mg and used for at least 12 weeks were screened. 194 patients who met the inclusion criteria were included in the study. Inclusion criteria for the study; Patients who have not used empagliflozin before and have received empagliflozin treatment for at least 12 weeks, patients over the age of 18, patients under 75 years of age, patients who are not pregnant, those without acute infection, those who have not started antihyperlipidemia treatment in the last month and have not changed, and those who do not use drugs affecting the bone marrow, spleen-related disease, acute and chronic inflammatory disease and consists of people without a history of malignancy. Exclusion criteria; Type-1 DM, who use empagliflozin for less than 12 weeks, pregnant women and patients with chronic renal failure. Demographic data, comorbidities and diabetes medication used before empagliflozin were noted. Glucose, hemoglobin A1c (HbA1c), HDL-C, low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and hemogram parameters were recorded before and after empagliflozin.

This study was approved by the university/local human research ethics committee, and all procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

Statistical Analysis

IBM SPSS 22 program was used for data analysis and statistical analysis. Student's T test was used for intergroup comparisons of normally distributed parameters as well as descriptive statistical methods (mean, standard deviation, ratio) when evaluating study data; Mann-Whitney U test was used for the intergroup comparisons of non-normally distributed parameters. In addition, Wilcoxon Signed Rank test was used. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

RESULTS

A total of 194 patients, 86 male and 108 female, using empagliflozin were included in our study. The mean age was 63.12±4.12 in men and 64.26±5.90 in women. The duration of DM was 13.05±5.34 in men and 14.09±6.01 in women. DM drugs used before empagliflozin, comorbidities and complications of DM are shown in **Table 1.**

Table 1. Demographic and clinical data of the patients

Sex=n (%)	
Male	86 (44.3)
Female	108 (55.6)
Age (years)±SD	
Male	63.12±4.12
Female	64.26±5.90
Disease duration (years) ± SD	
Male	13.05±5.34
Female	14.09±6.01
Comorbidity (n)	
Hypertension	105
Hyperlipidemia	47
Coronary artery disease	31
Cerebrovascular disease	7
None	64
DM medication before empagliflozin(n)	
Insulin	75
Metformin	49
Linagliptin	24
Vildagliptin	28
Pioglitazone	27
Other	10
DM microvascular complications(n)	
None	94
Neuropathy	39
Nephropathy	29
Retinopathy	32

Plasma fasting glucose, HbA1c, LDL-C, NLR and MHR values of T2DM patients after empagliflozin treatment were statistically significantly decreased compared to pre-treatment with empagliflozin ($p<0,05$). HDL-C value, on the other hand, increased significantly after empagliflozin ($p<0,05$) (**Table 2**).

There was no statistically significant difference in blood parameters of T2DM patients with neuropathy after using empagliflozin ($p>0,05$) (**Table 3**).

Table 2. Comparison of biochemical and hemogram parameters of T2DM patients before and after empagliflozin

	Before Empagliflozin Mean±SD	After Empagliflozin Mean±SD	p
Plasma fasting glucose (mg/dL)	188.02±63.80	146.69±57.04	<0.001*
HbA1c (%)	8.24±1.83	6.37±1.43	<0.001*
Triglyceride (mg/dl)	208.51±72.28	192.60±60.17	0.063
Total Cholesterol (mg/dl)	173.66±52.73	171.72±49.24	0.071
HDL-C (mg/dl)	41.82±11.83	46.64±13.61	0.003*
LDL-C(mg/dl)	108.91±37.27	101.87±43.28	0.041*
ALT (IU/L)	23.19±11.41	24.18±13.06	0.073
AST (IU/L)	20.93±6.93	21.22±9.54	0.967
White blood cell	8.55±4.64	8.40±3.48	0.816
Hemoglobin (g/dl)	13.08±4.07	13.87±2.27	0.163
Neutrophil(10^3/mm^3)	5.01±1.38	4.93±1.19	0.263
Lymphocyte (10^3/mm^3)	2.62±0.43	2.67±0.58	0.107
Monocyte (10^3/mm^3)	0.49±0.11	0.50±0.73	0.473
NLR	1.92±0.63	1.74±0.78	0.002*
MHR	0.01171±0.00401	0.01072±0.00941	0.042*
Platelet (10^3/mm^3)	298.76±72.34	287.09±71.23	0.118

*p<0.05, SD: standard deviation

Table 3. Comparison of biochemical and hemogram parameters of T2DM patients with diabetic neuropahty before and after empagliflozin

	Before Empagliflozin Mean±SD	After Empagliflozin Mean±SD	p
Plasma fasting glucose (mg/dL)	196.96±54.82	183.69±47.03	0.634
HbA1c (%)	10.04±1.97	9.61±1.23	0.072
Triglyceride (mg/dl)	188.71±62.38	184.59±61.24	0.963
Total Cholesterol (mg/dl)	182.31±46.28	171.81±47.28	0.821
HDL-C (mg/dl)	40.36±10.47	43.75±11.58	0.053
LDL-C (mg/dl)	107.99±34.53	108.78±36.41	0.061
NLR	3.69±0.99	3.36±0.78	0.072
MHR	0.01611±0.00321	0.01539±0.00611	0.143

SD: standard deviation

DISCUSSION

In our study, after empagliflozin treatment in T2DM patients, plasma fasting glucose, HbA1c, LDL-C, NLR and MHR values decreased significantly, while HDL-C values increased significantly. The prevalence of type 2 diabetes mellitus has doubled over the past 3 decades and is likely to affect a half a billion people in the next 3 decades (10). Female gender and advanced age are predisposing factors for T2DM (11). Of the patients participating in our study, 55.6% were female and 44.3% were male. The mean age was found to be 64.01 years.

Sodium glucose cotransporter 2 (SGLT2) inhibitors have a unique mecha-nism of action leading to excretion of glucose in the urine and subsequent lowering of plasma glu-cose. This mechanism is independent of β-cell function; thus, these agents are effective treatment for type 2 diabetes mellitus (T2DM) at theoretically any disease stage. Empagliflozin is one of three approved SGLT2 inhibitors (12). In a study by Rosenstock et al. (13) a statistically significant decrease was found in HbA1c, fasting plasma glucose and body weight after 12 weeks of empagliflozin treatment. In our study, similar to the literature, a statistically significant decrease was found in the fasting plasma glucose and HbA1c averages of the patients after empagliflozin (p<0.001).

SGLT2 inhibitors reduce body weight and visceral adiposity, and improve various metabolic abnormalities associated with metabolic syndrome such as blood pressure, lipid profile, and serum uric acid level (14). SGLT2 inhibitors are associated with a small increase in HDL-C as well as an increase in LDL-C with concomitant reductions in triglyceride levels (15,16). In addition, a meta-analysis of 34 randomized controlled trials showed that the administration of SGLT2 inhibitors increased HDL-C (mean difference 1.93 mg/dL), LDL-C (mean difference 3.5 mg/dL) and decreased serum triglycerides (mean difference 7.8 mg/dL) (17). In the comparison study of empagliflozin 10mg, empagliflozin 25mg and placebo by Hach et al. (18) small increases in HDL-cholesterol and LDL-cholesterol and a small decrease in triglyceride levels were observed in the empagliflozin group. In our results, there was a significant increase in HDL-C and a significant decrease in LDL-C (HDL-C p:0.003, LDL-C p:0.041), while the decrease in triglyceride level was not

statistically significant (p:0.063). In a retrospective study by Yuya et al. (19) in non-alcoholic fatty liver patients, patients using dipeptidyl peptidase-4 inhibitor and SGLT2 inhibitor for 24 weeks were analyzed. Decreases in transaminase activities were found to be similar in both groups. We did not detect any significant changes in AST and ALT values before and after empagliflozin.

MHR and NLR values are used as markers of inflammation in diabetic patients (20,21). There are studies showing the anti-inflammatory and antioxidant properties of empagliflozin treatment in T2DM patients (22,23). However, we could not find any study in the literature investigating the effect of empagliflozin treatment on MHR and NLR levels. Chronic inflammatory disorders and dyslipidemia in type 2 diabetes mellitus (T2DM) are essential contributors to the development of atherosclerotic cardiovascular disease. High NLR and MHR values are associated with cardiovascular disease in T2DM patients (24,25). Cardiovascular mortality is the principal cause of death in individuals with T2DM. The recently published Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study demonstrated that in T2DM patients with high cardiovascular disease risk empagliflozin reduced the primary major adverse cardiac event end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) by 14% (26). In our study, a significant decrease was found in NLR and MHR values after empagliflozin (NLR p:0.002, MHR p:0.042).

Up to 50% of diabetes patients suffer from microvascular complications, including diabetic peripheral neuropathy, diabetic retinopathy and diabetic kidney disease (27,28). There are also evidences that inflammation may play a key role in occurrence of microvascular complications This result shows us that NLR and MHR should be used as inflammation markers in patients using empagliflozin. (24,29,30). In addition, oxidative stress plays a strong role in the pathogenesis of diabetic complications (31). In the study of the effect of empagliflozin on diabetic microvascular complications, Eid et al. (32) did not find any effect on neuropathy in T2DM subjects. In the study of Mehta et al. (33) patients using empagliflozin did not detect any difference in the improvement of diabetic neuropathy when compared to patients using other oral antihyperglycemic drugs. In our study, we did not find any changes in the biochemical and hemogram parameters of diabetic neuropathy patients using empagliflozin in accordance with the literature.

CONCLUSION

Empagliflozin's decrease in NLR and MHR in type 2 DM patients shows that it provides anti-inflammatory activity in these patients

Limitation

This study has some limitations.

1. It is not known that the patients took antidiabetic drugs regularly before empagliflozin
2. Whether the drug use is regular after empagliflozin treatment
3. Failure to evaluate diabetic neuropathic complaints and findings after empagliflozin

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Medical Faculty Non-interventional Clinical Researchs Ethics Committee (Date: 29.12.2021, Decision No: 2021-88).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. J Levine M. Empagliflozin for type 2 diabetes mellitus: an overview of phase 3 clinical trials. Curr Diab Rev 2017; 13: 405-23.
2. Xu T, Weng Z, Pei C, et al. The relationship between neutrophil-to-lymphocyte ratio and diabetic peripheral neuropathy in type 2 diabetes mellitus. Medicine (Baltimore) 2017; 96: 8289.
3. Liu S, Zheng H, Zhu X, Mao F, Zhang S, Shi H. Neutrophil-to-lymphocyte ratio is associated with diabetic peripheral neuropathy in type 2 diabetes patients. Diabetes Res Clin Pract 2017; 130: 90-7.
4. De Rooij SR, Nijpels G, Nilsson PM, Nolan JJ, Gabriel R, Bobbioni-Harsch E. Low-grade chronic inflammation in the relationship between insulin sensitivity and cardiovascular disease (RISC) population: associations with insulin resistance and cardiometabolic risk profile. Diabetes Care 2009; 32: 1295-301.
5. Qiao S, Gao W, Guo S. Neutrophil–lymphocyte ratio (NLR) for predicting clinical outcomes in patients with coronary artery disease and type 2 diabetes mellitus: a propensity score matching analysis. Therapeutics and Clinical Risk Management 2020; 16: 437-43.
6. You S, Zhong C, Zheng D, Xu J, Zhang X, Liu H. Monocyte to HDL cholesterol ratio is associated with discharge and 3-month outcome in patients with acute intracerebral hemorrhage. J Neurol Sci 2017; 372: 157-61.
7. Vural G, Gümüsyayla Ş. Monocyte-to-high density lipoprotein ratio is associated with a decreased compound muscle action potential amplitude in patients with diabetic axonal polyneuropathy. Medicine 2018; 97: 12857.

8. Byrne NJ, Parajuli N, Levasseur JL, et al. Empagliflozin prevents worsening of cardiac function in an experimental model of pressure overload-induced heart failure. JACC Basic Transl Sci 2017; 2: 347–54.
9. Li C, Zhang J, Xue M, et al. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. Cardiovascr Diabetol 2019; 18: 1-13.
10. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat Rev Endocrinol 2011; 8: 228–36.
11. Diyabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Klavuzu. 2020: Türkiye Endokrinoloji ve Metabolizma Derneği.
12. J Levine M. Empagliflozin for type 2 diabetes mellitus: an overview of phase 3 clinical trials. Curr Diab Rev 2017; 13: 405-23.
13. Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes, Obesity and Metabolism 2013; 15: 1154-60.
14. Nagahisa T, Saisho Y. cardiorenal protection: Potential of sglt2 inhibitors and glp-1 receptor agonists in the treatment of type 2 diabetes. Diabetes Ther 2019; 10: 1733–52.
15. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014; 16: 457–66.
16. Hardy E, Ptanszynska A, de Bruin TWA. Changes in lipid profiles of patients with type 2 diabetes mellitus on dapagliflozin therapy. Diabetologia 2013; 56: 233.
17. Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N. SGLT2 inhibitors: a review of their antidiabetic and cardioprotective effects. Int J Environ Res Public Health 2019; 16: 2965.
18. Hach T, Gerich J, Salsali A, et al. Empagliflozin improves glycemic parameters and cardiovascular risk factors in patients with type 2 diabetes (T2DM): pooled data from four pivotal phase III trials. Diabetologie und Stoffwechsel 2014; 9: 142.
19. Seko Y, Sumida Y, Tanaka S, et al. Effect of sodium glucose cotransporter 2 inhibitor on liver function tests in Japanese patients with nonalcoholic fatty liver disease and type 2 diabetes mellitus. Hepatology Research 2017; 47: 1072-8.
20. Shiny A, Bibin YS, Shanthirani CS, et al. Association of neutrophillymphocyte ratio with glucose intolerance: an indicator of systemic inflammation in patients with type 2 diabetes. Diabetes Technol Ther 2014; 16: 524–30.
21. Onalan E. The relationship between monocyte to high-density lipoprotein cholesterol ratio and diabetic nephropathy. Pakistan J Med Sci 2019; 35: 1081-6.
22. Canet F, Iannantuoni F, Marañon AMD, et al. Does empagliflozin modulate leukocyte–endothelium ınteractions, oxidative stress, and ınflammation in type 2 diabetes? Antioxidants 2021; 10: 1228.
23. Singh RB, Fatima G, Kumar P, et al. Effects of empagliflozin on proinflammatory cytokines and other coronary risk factors in patients with type 2 diabetes mellitus: A single-arm real-world observation. Int J Clin Pharmacol Therapeutics 2021; 59: 17.
24. Wan H, Wang Y, Fang S, et al. Associations between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with diabetes: a cross-sectional study. J Diabetes Res 2020; 2020: 9.
25. Chen JW, Li C, Liu ZH, et al. The role of monocyte to high-density lipoprotein cholesterol ratio in prediction of carotid intima-media thickness in patients with type 2 diabetes. Frontiers in Endocrinology 2019; 10: 191.
26. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New Engl J Med 2015; 373: 2117-28.
27. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers 2019; 5: 41.
28. Winocour PH. Diabetes and chronic kidney disease: An increasingly common multi-morbid disease in need of a paradigm shift in care. Diabet. Med. 2018; 35: 300–5.
29. Öztürk ZA, Kuyumcu ME, Yesil Y, et al. Is there a link between neutrophil-lymphocyte ratio and microvascular complications in geriatric diabetic patients? J Endocrinol Invest 2013; 36: 593-9.
30. DiGangi C. Neutrophil-lymphocyte ratio: Predicting cardiovascular and renal complications in patients with diabetes. Journal of the American Association of Nurse Practitioners 2016; 28: 410-4.
31. Feldman EL, Nave KA, Jensen TS, Bennett DLH. New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. Neuron 2017; 93: 1296–313.
32. Eid S A, O'Brien PD, Hinder LM, et al. Differential effects of empagliflozin on microvascular complications in murine models of type 1 and type 2 diabetes. Biology 2020; 9: 347.
33. Mehta S, Nain P, Agrawal BK, et al. Effectiveness of empagliflozin with vitamin D supplementation in peripheral neuropathy in type 2 diabetic patients. Cureus 2021; 13: 12.