European Review for Medical and Pharmacological Sciences 2023; 27: 10577-10582

The effects of Dapagliflozin on monocyte-HDL ratio and neutrophil-lymphocyte ratio among patients with type-2 diabetes mellitus

Ü. SEN UZELI[1], M. DOĞAN[2]

[1]Department of Internal Medicine, Osmancık State Hospital, Çorum, Turkey
[2]Department of Internal Medicine, Hitit University Erol Olcok Training and Research Hospital, Corum, Turkey

Abstract. – OBJECTIVE: The present study attempted to explore the effects of starting dapagliflozin for glycemic control in Type-2 diabetes mellitus (DM) patients on the monocyte high-density lipoprotein ratio (MHR) and neutrophil-leukocyte ratio (NLO) as oxidative and inflammation markers.

PATIENTS AND METHODS: We retrospectively investigated the medical files of Type-2 DM patients administered dapagliflozin for at least 12 weeks. Then, we recorded the patients' demographics and compared their pre- and post-treatment biochemical and hemogram parameters.

RESULTS: We retrospectively evaluated the data of 210 patients. The results revealed that the levels of fasting blood glucose (FBG; $p < 0.001$), hemoglobin A1c (HbA1c; $p < 0.001$), high-density lipoprotein cholesterol (HDL-c; $p = 0.011$), triglyceride ($p = 0.002$), and monocytes ($p = 0.019$) and MHR ($p < 0.001$) significantly decreased among the patients following dapagliflozin treatment when compared to the pre-dapagliflozin period.

CONCLUSIONS: MHR is considered a practical, inexpensive inflammation marker for diabetics using dapagliflozin. However, we could not conclude NLR to be a significant inflammation marker, which, in turn, may suggest the need for comprehensive, prospective research.

Key Words:
Diabetes mellitus, Monocyte high-density lipoprotein ratio, Lymphocyte-monocyte ratio.

Introduction

Diabetes is a complex chronic metabolic disorder that affects many organs, resulting from absolute or partial insulin deficiency or resistance to the effect of insulin in peripheral tissues[1]. The development of acute and chronic diabetes-related complications is often associated with prolonged exposure to hyperglycemia[2]. Chronic inflammation predominantly occupies the pathogenesis of diabetes and the emergence of microvascular and macrovascular chronic complications[3]. Previous research[4] reported that diabetic patients present with high levels of plasminogen activator inhibitor 1 (PAI-1), chemotactic pro-inflammatory cytokines (chemokines), white blood cell count (WBC), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and C-reactive protein (CRP).

Neutrophil lymphocyte ratio (NLR), one of the complete blood count values, is used as a systemic inflammatory marker with the advantages of being easy to study and low costs[5,6]. Recent studies[7] have shown that NLR is a new inflammatory marker used for diabetes. It has been determined that diabetics with high NLR have poor glycemic control.

There are studies[8] in the literature showing that high NLR value can be used as a predictor in the development of chronic complications. On the other hand, it is known that HDL inhibits the expression of inflammatory adhesion molecules in endothelial cells through cytokines. It was previously suggested[9,10] that HDL inhibits monocyte activation as well as many antiatherosclerotic effects. Recently, the monocyte-high-density lipoprotein cholesterol (HDL-c) ratio (MHR) has been defined as a novel marker of chronic inflammation and oxidative stress, possibly thanks to the pro-inflammatory effect of monocytes as well as the antioxidant and anti-inflammatory effect of HDL-c. In this regard, the literature documented MHR to be significantly higher in diabetic patients developing microvascular complications compared to others. Besides, some studies[11,12] adopted MHR to identify if atherosclerosis and inflammation are involved in the etiopathogenesis of cerebrovascular and cardiovascular diseases.

Recognized as one of the sodium-glucose co-transporter 2 (SGLT-2) inhibitors, dapagliflozin is an antihyperglycemic agent following metformin in blood glucose control independent

Corresponding Author: Ülkem Şen Uzeli, MD; e-mail: ulkem_sen@hotmail.com

of insulin. It exhibits its effects by reducing glucose reabsorption in the renal proximal tubule and elevating glucose excretion through the urinary tract. It contributes to body weight, blood pressure, lipid profile, and uric acid levels. Moreover, its renoprotective and cardioprotective effects are indispensable[13]. In our study, we aimed to investigate the effect of dapagliflozin on MHR and NLR as markers of glycemic control and inflammation in Type-2 diabetes mellitus (DM) patients.

Patients and Methods

In this study, we retrospectively investigated the data of patients who presented to our internal medicine outpatient clinic with the diagnosis of Type-2 DM between 01.01.2020 and 01.31.2023, were started on dapagliflozin 10 mg, and used it for at least 12 weeks. We targeted to include those not using dapagliflozin before but receiving dapagliflozin treatment for at least 12 weeks after applying to our clinic, without pregnancy, being aged between 18-75 years, without acute infection, not receiving antihyperlipidemic treatment (if receiving, those not being started on the treatment within the last month or continuing the current treatment), not using medications affecting the bone marrow, and without a history of spleen disorder, acute and chronic inflammatory disease, and malignancy. However, we excluded those with Type-1 DM, using dapagliflozin for less than 12 weeks, pregnant, out of the age range of 18-75 years, with a picture of acute infection, with transaminase levels above five times, with a history of malignancy, being started on antihyperlipidemic medication within the last month, and with hematological disease. Accordingly, we investigated the data of 210 patients satisfying our inclusion criteria. Then, we utilized the hospital information management system to extract the patients' demographics, comorbidities, antihyperglycemic agents they used before dapagliflozin, hemogram parameters at the start and after 12 weeks of dapagliflozin use, and their levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, hemoglobin A1c (HbA1C), total cholesterol, triglyceride, HDL-c, and low-density lipoprotein cholesterol (LDL-c). The Non-Invasive Clinical Research Ethics Committee of the Faculty of Medicine of Hitit University granted ethical approval to our study (No.: 2023-63, dated 06.14.2023), and we carried out all procedures following the ethical principles in the Declaration of Helsinki.

Statistical Analysis

We present descriptive statistics as number (n), percentage (%), mean ± standard deviation (M±SD), median (Mdn), minimum (min), maximum (max), and interquartile range (IQR). We resorted to the Kolmogorov-Smirnov test to check the normality of the pre- and post-treatment data. Accordingly, we performed group comparisons using the Wilcoxon signed-rank test. The data were analyzed on IBM SPSS Statistics Standard Concurrent User V. 26 (IBM Corp., Armonk, NY, USA), and a p-value < 0.05 was accepted as statistically significant.

Results

The mean age of the patients, 127 (60.5%) females and 83 (39.5%) males, was found to be 60.1±8.8 years (30-74 years). The duration of DM was 13.14±5.38 in men and 14.15 ± 6.13 in women. We discovered hypertension (HT) in 126 (60.0%) patients, chronic obstructive pulmonary disease (COPD) in 21 (10.0%), coronary artery disease (CAD) in 42 (20.0%), cerebrovascular disease (CVD) in 4 (1.9%), hyperlipidemia in 28 (13.3%), and other diseases in 13 (6.2%). We also detected the use of insulin in 56 (26.7%) patients, metformin in 175 (83.3%), sulfonylurea in 68 (32.4%), pioglitazone in 26 (12.4%), and dipeptidyl peptidase-4 inhibitor (DPP-4) in 87 (41.4%; Table I).

Our findings suggested that post-treatment levels of fasting blood glucose (FBG) and HgA1c among the patients were significantly lower than the pre-treatment ($p < 0.001$ for both). Nevertheless, this was not the case for AST and ALT levels. While the patients' HDL levels after the treatment were significantly higher than before the treatment ($p = 0.001$), their pre-treatment LDL levels remained almost similar following the treatment. Although the patients' triglyceride levels after dapagliflozin treatment were statistically lower than levels before the treatment ($p < 0.001$), we could not conclude significant differences between pre- and post-treatment by their cholesterol, HGB, and WBC values. Besides, we found that platelet and monocyte values were significantly lower after dapagliflozin treatment than before the treatment ($p = 0.05$ and 0.02, respectively). While there was no significant change in the patients' neutrophil levels before and after dapagliflozin treatment, their lymphocyte levels and MHR values after the treatment were significantly decreased ($p < 0.001$). Finally, we discovered

their NLR values were significantly higher after dapagliflozin treatment ($p = 0.02$; Table II).

Discussion

Our results showed a significant reduction in the patients' FBG, HbA1c, triglyceride levels, and MHR after dapagliflozin treatment. Yet, it was vice versa for their LDL-c levels and NLR. The prevalence of diabetes has doubled in the last 30 years, and it is predicted1 that there will be about 700 million diabetics by 2045. Advanced age and female sex are significant predisposing factors for diabetes[1]. With a mean age of 62 years, while 60.5% of the participating patients were females, 39.5% were males. On the other hand, in their study investigating the prevalence of comorbidities in diabetic patients, Iglay et al[14] discovered HT in 82.1% of the patients, hyperlipidemia in 77.2%, and cardiovascular diseases in 21%. In our study, we found HT in 60% of the patients, hyperlipidemia in 13.3%, COPD in 10%, CAD in 20%, and CVD in 1.9%.

Sodium-glucose inhibitors block renal glucose reabsorption and boost urinary glucose excretion, which, in turn, decreases blood glucose and glycosylated hemoglobin values. They are utilized separately from insulin in all phases of Type-2 DM because they demonstrate their effects without relying on beta cell function and have no fading effects over time. Wilding et al[15] divided 808 patients using 30 U or more of insulin (as monotherapy or in combination with oral anti-diabetics) into four

Table I. Patients' Demographic Characteristics (n = 210).

	n	%
Sex		
Female	127	60.5
Male	83	39.5
Age, (years)*	60.1±8.8 (30-74)*	
Disease Duration (years)±SD		
Female	14.15±6.13	
Male	13.14±5.38	
BMI (kg/cm²)		
Female	26.9 (24.9-28.5)	
Male	25.8 (24.1-27.9)	
Comorbidities**		
Hypertension	126	60.0
COPD	21	10.0
CAD	42	20.0
CVD	4	1.9
Hyperlipidemia	28	13.3
Other	13	6.2
Medications**		
Insulin	56	26.7
Metformin	175	83.3
Pioglitazone	26	12.4
DDP4-İ	87	41.4
Other	68	32.4

n: Number of patients, %: Percentage, *M±SD (min-max), **More than one response may be available. BMI: Body Mass Index COPD: Cronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, CVD: Cerebrovascular Disease, DDP4-I: Dipeptidil Peptidaz-4 Inhibitor.

Table II. Pre- and Post-Treatment Comparisons of Patients' Laboratory Values.

	Measurement		Test statistics†	
	Pre-treatment	Post-treatment	*z*	*p*
FBG (mg/dL)	197.50 (85.25)	163.50 (71.50)	7.230	**<0.001**
HgA1c (%)	9.30 (2.33)	8.50 (2.03)	8.774	**<0.001**
AST (IU/L)	16.00 (8.50)	17.00 (8.00)	0.181	0.857
ALT (IU/L)	18.00 (11.25)	18.00 (11.00)	1.140	0.254
HDL (mg/dL)	45.50 (14.25)	46.00 (15.00)	3.400	**0.001**
LDL (mg/dL)	103.50 (48.25)	109.00 (49.25)	0.083	0.933
Triglyceride(mg/dL)	168.50 (102.00)	155.50 (98.50)	3.031	**0.002**
Total Cholesterol(mg/dL)	185.50 (49.75)	182.00 (51.00)	1.833	0.067
Hemoglobin (g/dl)	13.60 (1.80)	13.70 (1.80)	1.801	0.072
White blood cell	7,770.0 (2,495.0)	7,515.0 (2,812.0)	0.020	0.984
Platelet (10^3/mm^3)	268.50 (88.75)	256.00 (90.00)	1.962	**0.049**
Monocyte (10^3/mm^3)	580.00 (232.50)	530.00 (232.50)	2.355	**0.019**
Neutrophil (10^3/mm^3)	4,345.0 (1,967.5)	4,385.0 (2,077.5)	1.873	0.061
Lymphocyte (10^3/mm^3)	2,445.0 (1,050.0)	2,310.0 (1,042.5)	2.549	**0.011**
MHR	12.75 (8.39)	11.81 (7.35)	4.005	**<0.001**
NLR	1.65 (0.94)	1.88 (1.17)	2.239	**0.025**

Data are presented as median values (interquartile ranges). †: Wilcoxon signed-rank test. FBG: Fasting blood glucose, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, HDL: High-density LSipoprotein, LDL: Low-Density Lipoprotein, MHR: Monocyte-HDL Ratio, NLR: Neutrophil Lymphocyte Ratio

groups, added placebo and 2.5 mg, 5 mg, and 10 mg dapagliflozin, respectively, to their current treatment for 24 weeks, and traced the reduction in their insulin requirement. The results documented significant decreases in the mean daily insulin requirement and HbA1c values of the treatment group based on basal values compared to the placebo group. Similarly, Ferrannini et al[16] added 2.5 mg, 5 mg, and 10 mg dapagliflozin to the regime for 24 weeks in Type-2 DM patients whose glycemic control could not be achieved through specific dietary regimes and exercises and concluded 15 mg/dL, 24 mg/dL and 28 mg/dL decreases in their FBG levels, respectively, compared to the placebo group. Overlapping with previous findings, we also detected significant decreases in the patients' FBS and HbA1c levels after dapagliflozin treatment.

Previous research[17] has often reported that dapagliflozin lowers body weight by reducing both visceral and subcutaneous adipose tissues and regulates metabolic parameters (e.g., blood pressure). Moreover, SGLT-2 was previously found[18,19] to contribute to LDL-c and HDL-c levels but reduces triglyceride levels. In a study conducted by Yaribeygi et al[18], it was stated that SGLT-2 inhibitors could control dyslipidemia by increasing lipolysis. Calapkulu et al[19] discovered that patients had a 13.4 mg/dL increase in LDL-c levels and a 25.9 mg/dL decrease in triglyceride levels after six months of dapagliflozin treatment. Similarly, Gurkan[20] observed an increase of 11.53 mg/dL (8.68%) in LDL-c levels and a decrease of 43.04 mg/dL (19.58%) in triglyceride levels among patients. Consistent with these findings, we detected a significant increase in the patients' HDL-c levels ($p = 0.001$) and a decrease in their triglyceride levels ($p = 0.002$) after 12 weeks of dapagliflozin treatment. Besides, Seko et al[21] retrospectively analyzed the data of patients with non-alcoholic fatty liver disease using DPP-4 and SGLT-2 inhibitors for 24 weeks and found the decreases in transaminase activities to be similar in both groups. In our study, we could also not find a significant change in the patients' transaminase levels before and after dapagliflozin treatment, overlapping with the previous findings[22].

In a study[23] on patients with a new diagnosis of fibromyalgia, including 127 patients, monocyte level and MHR were found to be higher than healthy individuals. As mentioned in previous studies[6,24], MHR and NLR are adopted as inflammation markers in diabetic patients as well as in all chronic diseases. In a study[25] conducted with prediabetes and diabetes patients, it was stated that the neutrophil/lymphocyte ratio was significantly higher in diabetic patients compared to healthy and prediabetes patient groups. The literature hosts studies[26] have reported that dapagliflozin functions as an anti-inflammatory in Type-2 DM patients. While there are papers in literature where SGLT-2 inhibitor empagliflozin adopts MHR as an anti-inflammatory and antioxidant marker and studies showing if NLR can be adopted as an anti-inflammatory marker, dapagliflozin seems to be missing. On the other hand, cardiovascular diseases are considered[27] significant causes of mortality and morbidity in the diabetic population. Chronic inflammatory disorders and dyslipidemia are the primary contributors to the development of atherosclerotic cardiovascular disease in Type-2 DM.

In turn, higher NLR and MHR were previously shown[28,29] to be associated with cardiovascular disease in Type-2 DM patients. Moreover, it was reported that NLR increases in cases of prediabetes and diabetes and that increased NLR is associated with subclinical and overt atherosclerotic coronary heart disease (ACHD) in diabetic patients[30,31]. Besides, in the DECLARE-TIMI 58 trial[32] (The Design and Rationale for the Dapagliflozin Effect on Cardiovascular Events), dapagliflozin was found to reduce hospitalizations for heart failure and cardiovascular deaths in patients with Type 2 DM and high cardiovascular risk when compared to placebo. In our study, while we found a significant decrease in MHR after dapagliflozin treatment ($p < 0.001$), NLR did not decrease significantly among the patients, overlapping with some previous results[33].

Our study was conducted as a retrospective study. Therefore, the desired equality could not be achieved in terms of the gender ratios of the patients included in the study.

Conclusions

We concluded that dapagliflozin lowered MHR in Type 2 DM patients, which may be a hallmark of its anti-inflammatory activity in these patients. Nevertheless, a larger, prospective research is still needed to confirm our findings on NLR.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

The study was carried out with the permission of Hitit University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (No.: 2023-63, dated 06.14.2023).

Funding
The authors received no financial support for this article's research, authorship, and publication.

Informed Consent
Not applicable due to the retrospective nature of the study.

Authors' Contribution
Uzeli Sen Ülkem: Project development, research design, manuscript reviewing, writing, editing, and revising. Doğan Murat: Project development, research design, manuscript reviewing, writing, editing, and revising. Both authors approved the final version of the study.

Data Availability
The data are available upon request.

ORCID ID
Ülkem Şen Uzeli: 0009-0006-6479-7858
Murat Doğan: 0000-0003-0457-2025

References

1) Satman İ, İmamoğlu Ş, Yılmaz C, Dinççağ N. Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi Ve İzlem Kılavuzu. Miki Matbacılık: Türkiye Endokrinoloji ve Metabolizma Derneği, Ankara, Mayıs 2014: 15-25.
2) Levine MJ. Empagliflozin for type-2 diabetes mellitus: an overview of phase 3 clinical trails. Curr Diabetes Rev 2017; 13: 405-423.
3) Liu S, Zheng H, Zhu X, Mao F, Zhang S, Shi H, Li Y, Lu B. Neutrophil-to-lymphocyte ratio is associated with diabetic peripheral neuropathy in type 2 diabetes patients. Diabetes Res Clin Pract 2017; 130: 90-97.
4) Verdoia M, Schaffer A, Barbieri L, Aimaretti G, Marino P, Sinigaglia F, Suryapranata H, Deluca G. Impact of diabetes on neutrophil-to-lymphocyte ratio and its relationship to coronary artery disease. Diabetes Metab 2015; 41: 304-311.
5) Doğan M, Boyacıoğlu M, Doğan AG. Evaluation of neutrophyl/lymphocyte ratio, platelet/lymphocyte ratio and mean platelet volume according to the disease activity index in patients of ankylosing spondylitis. JHSM 2022; 5: 247-251.
6) Shiny A, Bibin YS, Shanthirani CS, Regin SB, Anjana MR, Balasubramanyam M, Jebarani S, Mohan V. Association of neutrophil-lymphocyte ratio with glucose intolerance: an indicator of systemic inflammation in patients with type 2 diabetes. Diabetes Technol Ther 2014; 16: 524-530.
7) Moursy EY, Megallaa MH, Mouftah RF, Ahmed SM. Relationship between neutrophil lymphocyte ratio and microvascular complications in Egyptian patients with type 2 diabetes. Am J Inter Med 2015; 3: 250-255.
8) Hussain M, Babar MZM, Ahtar L, Hussain MS. Neutrophil lymphocyte ratio (NLR): A well assessment tool of glycemic control in type 2 diabetic patients. Pak J Med Sci 2017; 33: 1366-1370.
9) Murphy AJ, Woollard KJ, Hoang A, Mukhamedova N, Stirzaker RB, McCormick SP, Remaley AT, Sviridov D, Dusting JC. High-density lipoprotein reduces the human monocyte inflammatory response. Arterioscler Thromb Vasc Biol 2008; 28: 2071-2077.
10) Cockerill GW, Rye K-A, Gamble JR, Vadas MA, Barter PJ. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler Thromb Vasc Biol 1995; 15: 1987-1994.
11) You S, Zhong C, Zheng D, Xu J, Zhang X, Liu H, Zhang Y, Shi J, Huang Z, Cao Y, Liu CH. Monocyte to HDL cholesterol ratio is associated with discharge and 3-month outcome in patients with acute intracerebral hemorrhage. J Neurol Sci 2017; 372: 157-161.
12) Canpolat U, Çetin EH, Cetin S, Aydin S, Akboga MK, Yayla C, Turak O, Aras D, Aydoğdu S. Association of monocyte-to-HDL cholesterol ratio with slow coronary flow is linked to systemic inflammation. Clinical Appl Thromb Hemost 2016; 22: 476-482.
13) Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N. SGLT2 Inhibitors: A Review of Their Anti-diabetic and Cardioprotective Effects. Int J Environ Res Public Health 2019; 16: 2965.
14) Iglay K, Hannachi H, Joseph Howie P, Xu J, Li X, Engel SS, Moore LM, Rajpathak S. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. Current Med Res Opin 2016; 32: 1243-1252.
15) Wilding JP, Noorwood P, T'joen C, Bastien A, List JM, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers; applilicability of a novel ınsulin independent treatment. Diabetes care 2009; 32: 1656-1662.
16) Ferrannini E, ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with ınadequate glycemic control by diet and exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010; 33: 2217-2224.
17) Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC, Johansen GE. SGLT-2 inhibitörs and cardiovasküler risk: Proposed pathways and review and ongoing outcome trials. Diab Vasc Dis Res 2015; 12: 90-100.
18) Yaribeygi H, Maleki M, Reiner Ž, Jamialahmadi T, Sahebkar A. Mechanistic View on the Effects of SGLT2 Inhibitors on Lipid Metabolism in Diabetic Milieu. J Clin Med 2022; 11: 6544.
19) Calapoglu M, Cander S, Gul OO, Ersoy C. Lipid profile in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data of six months retrospective lipid profile from single center. Diabetes Metab Syndr 2019; 13: 1031-1034.

20) Gürkan E. Effects of Dapagliflozin on Serum Low-Density Lipoprotein Cholesterol and Triglyceride Levels. Eur J Ther 2020; 26: 76-80.
21) Seko Y, Sumida Y, Tanaka S, Mori K, Taketani H, Ishıba H, Hara T, Okajima A, Umemura A. Effect of sodium glucose co-transporter 2 inhibitor on liver function tests in Japanese patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus. Hepatol Res 2017; 47: 1072-1078.
22) Doğan M. The effect of empagliflozin on monocyte high-density lipoprotein ratio in patients with type 2 diabetes mellitus. Anatolian Curr Med J 2022; 4: 255-259.
23) Doğan AG. Evaluation of neutrophil-lymphocyte ratio, lymphocyte-monocyte, and monocyte-high density lipoprotein ratios in patients with fibromyalgia and determination of their relationship with disease activity, pain, and depression levels. Eur Rev Med Pharmacol Sci 2023; 27: 4929-4935.
24) Onalan E. The relationship between monocyte to high-density lipoprotein cholesteroratio and diabetic nephropathy. Pak J Med Sci 2019; 35: 1081-1086.
25) Klisić A, Šćepanović A, Kotur-Stevuljević J, Ninić A. Novel leukocyte and thrombocyte indexes in patients with prediabetes and type 2 diabetes mellitus. Eur Rev Med Pharmacol Sci 2022; 26: 2775-2781.
26) Wang C, Qin Y, Zhang X, Yang Y, Wu X, Liu J, Qin S, Chen K, Xiao W. Dapagliflozin on Indicators of Myocardial Fibrosis and Levels of Inflammatory Factors in Heart Failure Patients. Dis Markers 2022: 5834218.
27) Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat Rev Endocrinol 2011; 8: 228-236.
28) Wan H, Wang Y, Fang S, Chen Y, Zhang W, Xia F, Wang N, Lu Y. Associations between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with diabetes: a cross-sectional study. J Diabetes Res 2020; 2020: 9.
29) Chen JW, Li C, Liu ZH, Shen Y, Ding FH, Shu XY, Zhang RY, Shen WF, Lu L, Wang XQ. The role of monocyte to high-density lipoprotein cholesterol ratio in prediction of carotid intima media thickness in patients with type 2 diabetes. Front Endocrinol 2019; 10: 191.
30) Mertoglu C, Gunay M. Neutrophil-Lymphocyte ratio and Platelet-Lymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. Diabetes Metab Syndr 2017; 11: 127-131.
31) DiGangi C. Neutrophil-lymphocyte ratio: Predicting cardiovascular and renal complications in patients with diabetes. J Am Assoc Nurse Pract 2016; 28: 410-414.
32) Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Bansilal S, Bhatt DL, Leiter LA, Mcguire DK, Wilding JP, Nilson IAG, Langkilde AM, Johansson PA, Sabatine MS. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. Am Heart J 2018; 200: 83-89.
33) Bas S, Türkmen FM. Changes in neutrophil-to-lymphocyte ratio following treatment with dapagliflozin in patients with type 2 diabetes mellitus. Gulhane Med J 2022; 64: 217-221.