The European Research Journal 2025;11(3):449-455 Original Article

DOI: https://doi.org/10.18621/eurj.1561505 *Internal Medicine*

Investigation of the effect of SGLT-2 inhibitors on the triglyceride/glucose index in diabetic patients: a cross-sectional study

Düriye Sıla Karagöz Özen[1], Abdülcelil Kayabaş[1], Rana İlhan Van[1], Mehmet Derya Demirağ[2]

[1]Department of Internal Medicine, Samsun Training and Research Hospital, Samsun Türkiye; [2]Department of Rheumatology, Samsun University, Samsun Training and Research Hospital, Samsun, Türkiye

ABSTRACT

Objectives: The aim of this study is to estimate the change in the Triglyceride Glucose Index (TyG index), in patients with type 2 Diabetes Mellitus who are using a sodium-glucose cotransporter-2 (SGLT2) inhibitor, and to evaluate the effect of these drugs on triglyceride glucose index.

Methods: This is a cross-sectional study of 55 diabetic patients in our internal medicine clinic in Turkey. Triglyceride, glucose, and glycosylated hemoglobin (HbA1c) values were measured at the beginning of the treatment and the 3rd-month follow-up. The TyG index of the patients before starting SGLT-2 inhibitor treatment and at the end of 3 months of treatment was calculated by the researchers using the data in the hospital digital records.

Results: The mean age of 55 patients (56.4% male) was 62.7±10.2 years. The number of patients using dapagliflozin 10 mg was 15 (27.3%) and the number of patients using empagliflozin was 41 (72.8%). It was determined that fasting plasma glucose, TyG index, and HbA1c values before starting SGLT-2 inhibitor treatment and in the 3rd month of treatment decreased significantly (P<0.001, P=0.002 and P<0.001, respectively). According to the correlation analysis results between TyG index and HbA1c, it was determined that the values both before treatment and in the 3rd month of treatment showed a correlation (r=0.516, P<0.001 and r=0.448, P=0.001, respectively).

Conclusions: SGLT-2 inhibitor usage significantly reduces TyG index in diabetic patients, and new studies are needed to investigate the effect of these drugs on triglyceride index among pre-diabetic patients.

Keywords: Triglyceride glucose index, SGLT-2 inhibitor, dapagliflozin, empagliflozin, diabetes mellitus

The Triglyceride Glucose Index (TyG index) was first proposed in Mexico in 2008 as a marker for insulin resistance [1]. The formula for its calculation is "ln [Fasting triglyceride (mg/dL) × fasting glucose (mg/dL)]/2". The initial cut-off for the TyG index was Ln 4.65 to diagnose insulin resistance, with an initial sensitivity of 84.0% and specificity of 45.0% [1]. Subsequent research validated its effectiveness, showing a higher sensitivity when compared to the gold standard test [2]. Later studies have indicated that the TyG index is more accurate than the Homeostatic Model Assessment for In-

Received: October 4, 2024 **Accepted:** January 13, 2025 **Available Online:** February 14, 2025 **Published:** May 4, 2025

How to cite this article: Karagöz Özen DS, Kayabaş A, İlhan Van R, Demirağ MD. Investigation of the effect of SGLT-2 inhibitors on the triglyceride/glucose index in diabetic patients: a cross-sectional study. Eur Res J. 2025;11(3):449-455. doi: 10.18621/eurj.1561505

Corresponding author: Düriye Sıla Karagöz Özen, MD., Assoc. Prof., Phone: +90 362 311 15 00, E-mail: silakaragoz@yahoo.com.

sulin Resistance (HOMA-IR) in predicting metabolic syndrome (MetS) [3] and is uniquely effective in predicting the onset of MetS [3].

The relationship between the TyG index and atherosclerotic cardiovascular disease has been the subject of extensive research. A notable study involving two large cohorts found that rising values of the TyG index were linked to an elevated risk of heart failure. Specifically, those in the maximum one-fourth of the TyG index had an adjusted increased risk significantly when compared to the lowest (P<0.001) [4]. In another study, the investigators found that a higher TyG index was an independent predictive factor for coronary artery disease (CAD) severity among patients with glucose intolerance or impaired fasting glucose [5]. This study found that individuals in the highest TyG index group (≥7.38) had an approximately 1.5 times elevated risk of multivessel CAD compared to those in the lowest group (<6.87) [5]. Additionally, a high TyG index was associated with a greater risk of atrial fibrillation in non-diabetic individuals [6].

Lee *et al*. [7] examined the relationship of the TyG index with coronary stenosis in a cohort of 888 diabetic patients with no previous CAD. Their findings indicated that elevated levels of TyG index were linked to a greater risk of coronary artery stenosis, alongside factors such as advanced age, male gender, poor glycemic control, longer diabetes duration, and non-use of statins. The study further established that a higher TyG index independently contributed to CAD risk (OR: 3.19, 95% CI: 1.371-7.424) [7].

Additional research has reinforced the positive association between elevated TyG index levels and atherosclerotic cardiovascular disease events, even after adjusting for confounding variables, in a population with a 10-year median follow-up period [8].

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, including dapagliflozin and empagliflozin, represent newer treatment options for Type 2 Diabetes Mellitus (T2DM) due to their glycosuric effects. Extensive research has demonstrated that these drugs not only enhance blood glucose control but also reduce mortality in heart failure patients [9, 10]. Several large studies have shown that SGLT-2 inhibitors can significantly lower the risk of cardiovascular morbidity and mortality, including heart attacks, strokes, and hospitalizations for heart failure, compared to placebo in people with a diagnosis of T2DM who have established cardiovascular disease or at high risk for cardiovascular disease. The mechanisms by which SGLT-2 inhibitors provide cardiovascular protection are not entirely clear but may be related to their ability to reduce blood glucose levels, blood pressure, and body weight, as well as improve cardiac function and metabolic parameters such as lipid profiles and kidney function. Recent studies also suggest that SGLT-2 inhibitors have protective effects against kidney failure and albuminuria [11, 12]. The mechanisms underlying their beneficial impact on endothelial function include increased nitric oxide production, reduced oxidative stress, improved microvascular function, and decreased inflammation [13].

Our study aims to assess changes in the TyG index among patients with a diagnosis of T2DM following the initiation of SGLT-2 inhibitor treatment.

METHODS

This cross-sectional study involved 55 patients over 18 years old, diagnosed with Type 2 Diabetes Mellitus, who were seen at the Internal Medicine outpatient clinic of Samsun Training and Research Hospital in Turkey. The data of patients who began SGLT-2 inhibitor treatment (dapagliflozin 10 mg, empagliflozin 10 mg, or empagliflozin 25 mg) and were monitored for at least 3 months from January 1, 2022, to December 31, 2022, were analyzed through a retrospective file review. The study adhered to the Declaration of Helsinki and was approved by the Samsun University Ethics Committee, with protocol number SUKAEK-2023 7/20. This study is also registered in Clinical Trials System with the protocol number NCT05915884. Exclusions were made for patients with insufficient follow-up, missing data, those receiving dyslipidemia treatment, or those who started other antidiabetic drugs during the study period. The patient selection is illustrated in Fig. 1.

All demographical and biochemical findings were collected anonymously from medical records, including age, gender, diabetes duration, SGLT-2 inhibitor usage duration, medical history, all medications for glucose control, dyslipidemia status, hypothyroidism status, and laboratory test results. Triglyceride, glucose, and glycosylated hemoglobin (HbA1c) levels were measured at the start of treatment and after 3

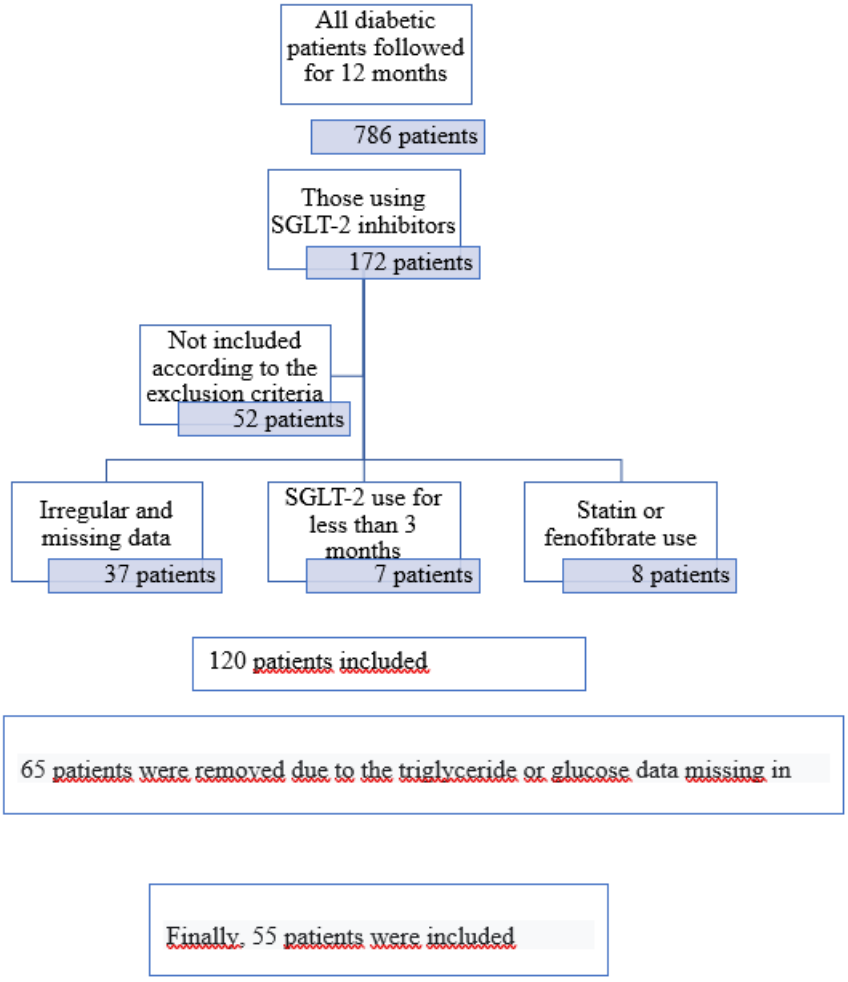

Fig. 1. Patient selection for inclusion.

months. The calculation of the TyG index was done according to the aforementioned formula [1]. No additional blood tests or laboratory analyses were conducted.

Statistical Analysis

The analyses were conducted using SPSS 21.0.0.1 for Windows (Statistical Package for the Social Sciences; IBM). The Kolmogorov-Smirnov test was employed to assess data distribution. Continuous variables were presented as either mean or median depending on their distribution pattern. Categorical variables were reported as frequencies (n) and percentages (%). The paired sample t-test and the Wilcoxon signed-rank test assessed group differences. A P value of less than 0.05 was deemed statistically significant. Pearson correlation test was conducted to explore the relationships between variables.

RESULTS

The data of 786 diabetic patients followed for 12-month periods in our internal medicine clinic were searched and 55 patients were included for the last analysis (Fig. 1).

The mean age of 55 patients (56.4% male) was 62.7±10.2 years and the median duration of SGLT-2 inhibitor use was 18 (3-60) months. The number of patients using dapagliflozin 10 mg was 15 (27.3%) and the number of patients using empagliflozin was 41 (72.8%). Forty-nine (89.1%) patients had a diagnosis of diabetes for more than 5 years. Demographical properties are shown in Table 1.

It was determined that fasting plasma glucose, triglyceride index, and HbA1c values before starting SGLT-2 inhibitor treatment and in the 3rd month of treatment decreased significantly (P<0.001, P=0.002,

and P<0.001, respectively) (Table 2). According to the correlation analysis results between triglyceride index and HbA1c, it was determined that the values both before treatment and in the 3rd month of treatment showed a correlation (r=0.516, P<0.001 and r=0.448; P=0.001, respectively).

Subgroup analyses were done according to the nephropathy status and CAD status of the patients. While the change in the TyG index was found to be significant in those without CAD (n=40, 95% CI: 0.087-0.299; P=0.001), the index change was not found to be significant in those with an established CAD (n=14, 95% CI: -0.157-0.365; P=0.403). Similarly, while the change in triglyceride glucose index was not found to be significant in patients with nephropathy (n=15), 95% CI: -0.21-0.19; P=0.940], the index change was found to be significant in patients without nephropathy (n=39, 95% CI: 0.11- 0.34; P<0.001).

Table 1. The general features the study population

Variables	Data
Demographics	
Age (years)	62.7±10.2
Gender, male	31 (56.4)
SGLT-2 inhibitor, n (%)	
Dapagliflozin 10 mg	15 (27.3)
Empagliflozin 10 mg	37 (67.3)
Empagliflozin 25 mg	3 (5.5)
Other antidiabetic treatments, n (%)	
DPP4 inhibitor	37 (67.3)
Long acting insulin analogue	21 (38.2)
Preprandial insulin analogue	6 (10.9)
Sulphonylurea	10 (18.2)
Pioglitazone	6 (10.9)
Complications and comorbidities, n (%)	
Retinopathy	12 (21.8)
Nephropathy	15 (27.3)
Neuropathy	16 (29.1)
Hypertension	39 (70.9)
Coronary artery disease	14 (25.1)
Cerebrovasculary disease	2 (3.6)

Data are shown as mean±standard deviation or n (%) where appropriate

DISCUSSION

In our study, we observed a notable reduction in fasting plasma glucose, LDL cholesterol, HbA1c, and the TyG index following three months of treatment with empagliflozin or dapagliflozin in patients with T2DM. As previously mentioned in the introduction section existing research has highlighted a strong correlation between higher TyG index levels and an elevated adverse cardiovascular event risk [4-6].

A large-scale prospective study with 62,443 participants evaluated the TyG index at four-year intervals. After a median observation period of 7.01 years, cardiovascular disease incidence was 4.05%. This study revealed that higher quartiles of change in the index were related to a higher risk of experiencing new cardiovascular events. Specifically, after adjusting for various confounding factors, the hazard ratios for the biggest quartile (Q4) compared to the smallest quartile (Q1) were approximately 1,4 for overall cardiovascular disease, stroke, and myocardial infarction [14]. Another investigation found a significant relationship between elevated TyG index levels and carotid atherosclerosis, assessed by common carotid artery intima-media thickness in patients who had suffered ischemic strokes, suggesting that this index could be a promising indicator for atherosclerosis [15]. Moreover, a large prospective study from China involving 138,620 participants found that an increment in the TyG index was linked to an elevated risk of heart failure [16]. An analysis of patients with premature onset CAD showed that those with major adverse cardiovascular events had significantly higher TyG index values compared to those without such events (8.94±0.52 vs. 8.72±0.57, P<0.001) [17]. A recent metaanalysis also supported the link between elevated TyG index levels and cerebrovascular disease [18].

Our research indicates that SGLT-2 inhibitor therapy is associated with a reduction in the TyG index. However, the impact of this reduction on cardiovascular event risk was not evaluated in our study due to its cross-sectional design and the absence of long-term

Table 2. Biochemical properties before and after SGLT-2 inhibitor treatment

Variable	Before SGLT-2 inhibitor treatment (n=55)	3rd month of SGLT-2 inhibitor treatment (n=55)	P value
Fasting glucose median (mg/dL)	180 (74.00-600.00)	152 (48.97-140.00)	**<0.001**
Triglyceride (mg/dL)	163 (62.00-433.00)	162 (52.00-441.00)	0.265
Low density lipoprotein (mg/dL)	99.50 (0.34)	91.00 (31.15)	0.051
Triglyceride glucose index	5.18 (0.34)	5.01 (0.32)	**0.002**
Glycosylated hemoglobin (%)	8.93 (1.98)	7.69 (1.10)	**<0.001**

Data are shown as mean±standard deviation or median (minimum-maximum) where appropriate

follow-up data.

The evidence supporting the TyG index as a predictor of insulin resistance and metabolic syndrome, combined with its association with cardiovascular disease risk, suggests it may be valuable for assessing cardiovascular risk in diabetic patients. Previous studies have demonstrated that SGLT-2 inhibitors reduce the atherosclerotic cardiovascular disease risk regardless of diabetes diagnosis, and have a positive effect on mortality and hospitalization rate [9-12].

The EMPA-REG OUTCOME trial showed that adding empagliflozin to standard therapy resulted in a 14% reduction in 3-point major adverse cardiac events, a 38% decrement in cardiovascular mortality, a 32% decrement in all-cause mortality, and a 35% decrement in heart failure hospitalization compared to placebo [9]. Additionally, empagliflozin improved diabetic nephropathy and reduced albuminuria [9]. In our study, SGLT-2 inhibitor usage was divided into 72.8% for empagliflozin and 27.2% for dapagliflozin. We believe that the lack of another new antidiabetic drug except SGLT-2 inhibitor or lipid-lowering medication between the initial and follow-up laboratory tests was sufficient to discover the impact of SGLT-2 inhibitors on these parameters. A strength of our study was the consideration of various confounding factors affecting biochemical metabolic parameters in our inclusion and exclusion criteria, though this led to a significant reduction in the number of participants in the final analysis, which is a notable limitation.

In two comparable studies conducted in our country, the influences of these drugs on metabolic parameters were evaluated with similar sample sizes to ours [19, 20]. One study reported significant reductions in weight, body mass index, waist circumference, and hip circumference after six months of empagliflozin use [19]. The other study also found significant decreases in body mass index and weight in patients treated with empagliflozin compared to pre-treatment levels and the control group [20].

In our study, the change in triglyceride index was not found to be significant among patients with a history of CAD and those who already developed nephropathy, while a significant decrease was observed in the opposite cases. This result shows that starting SGLT-2 inhibitors early, before complications develop, is metabolically important. However, studies with larger numbers of participants are needed to generalize the results.

SGLT-2 inhibitor treatment may change during follow-up period. For example, a patient may start dapagliflozin treatment than changed into empagliflozin, vice versa. That's why, we could not perform drug specific analysis. We think that new prospective studies are needed to investigate the effect of each molecule on TyG index, seperately.

CONCLUSION

The results we obtained in our study showed that treatment of diabetic patients with SGLT-2 inhibitors reduces the TyG index. We think that new studies should be conducted to research the impact of these drugs on the TyG index and the risk of developing MetS in non-diabetic individuals.

Ethical Statement

The study adhered to the Declaration of Helsinki

and was approved by the Samsun University Clinical Research Ethics Committee (Decision no: SUKAEK-2023 7/20 and date: 12.04.2023)

Authors' Contribution

Study Conception: DSKÖ, AK; Study Design: DSKÖ, AK; Supervision: DSKÖ, AK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: DSKÖ, AK, RİV; Statistical Analysis and/or Data Interpretation: DSKÖ, AK, RİV; Literature Review: DSKÖ, AK, RİV; Manuscript Preparation: DSKÖ, AK, RİV, MDD; and Critical Review: DSKÖ, MDD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Acknowledgements

The abstract of this study was presented as poster presentation at 24th European Congress of Internal medicine in 2024.
This study is also registered in Clinical Trials System with the protocol number NCT05915884.

Editor's note

All statements made in this article are solely those of the authors and do not represent the views of their affiliates or the publisher, editors, or reviewers. Any claims made by any product or manufacturer that may be evaluated in this article are not guaranteed or endorsed by the publisher.

REFERENCES

1. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord. 2008;6(4):299-304. doi: 10.1089/met.2008.0034.
2. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95(7):3347-3351. doi: 10.1210/jc.2010-0288.
3. Son DH, Lee HS, Lee YJ, Lee JH, Han JH. Comparison of triglyceride-glucose index and HOMA-IR for predicting prevalence and incidence of metabolic syndrome. Nutr Metab Cardiovasc Dis. 2022;32(3):596-604. doi: 10.1016/j.numecd.2021.11.017.
4. Li X, Chan JSK, Guan B, et al. Triglyceride-glucose index and the risk of heart failure: Evidence from two large cohorts and a mendelian randomization analysis. Cardiovasc Diabetol. 2022;21(1):229. doi: 10.1186/s12933-022-01658-7.
5. Wang X, Xu W, Song Q, et al. Association between the triglyceride-glucose index and severity of coronary artery disease. Cardiovasc Diabetol. 2022;21(1):168. doi: 10.1186/s12933-022-01606-5.
6. Chen S, Mei Q, Guo L, et al. Association between triglyceride-glucose index and atrial fibrillation: A retrospective observational study. Front Endocrinol (Lausanne). 2022;13:1047927. doi: 10.3389/fendo.2022.1047927.
7. Lee EY, Yang HK, Lee J, et al. Triglyceride glucose index, a marker of insulin resistance, is associated with coronary artery stenosis in asymptomatic subjects with type 2 diabetes. Lipids Health Dis. 2016;15(1):155. doi: 10.1186/s12944-016-0324-2.
8. Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martínez JA. The TyG index may predict the development of cardiovascular events. Eur J Clin Invest. 2016;46(2):189-197. doi: 10.1111/eci.12583.
9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720.
10. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. Circulation. 2019;139(11):1384-1395. doi: 10.1161/CIRCULATIONAHA.118.037778.
11. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-334. doi: 10.1056/NEJMoa1515920 12.
12. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 2019;7(8):606-617. doi: 10.1016/S2213-8587(19)30180-9.
13. Preda A, Montecucco F, Carbone F, et al. SGLT2 inhibitors: from glucose-lowering to cardiovascular benefits. Cardiovasc Res. 2024;120(5):443-460. doi: 10.1093/cvr/cvae047.
14. Wang A, Tian X, Zuo Y, et al. Change in triglyceride-glucose index predicts the risk of cardiovascular disease in the general population: a prospective cohort study. Cardiovasc Diabetol. 2021;20(1):113. doi: 10.1186/s12933-021-01305-7.
15. Miao M, Zhou G, Bao A, et al. Triglyceride-glucose index and common carotid artery intima-media thickness in patients with ischemic stroke. Cardiovasc Diabetol. 2022;21(1):43. doi: 10.1186/s12933-022-01472-1.
16. Xu L, Wu M, Chen S, et al. Triglyceride-glucose index associates with incident heart failure: A cohort study. Diabetes Metab. 2022;48(6):101365. doi: 10.1016/j.diabet.2022.101365.
17. Wu Z, Liu L, Wang W, et al. Triglyceride-glucose index in the prediction of adverse cardiovascular events in patients with premature coronary artery disease: a retrospective cohort study.

Cardiovasc Diabetol. 2022;21(1):142. doi: 10.1186/s12933-02201576-8.
18. Yan F, Yan S, Wang J, et al. Association between triglyceride glucose index and risk of cerebrovascular disease: systematic review and meta-analysis. Cardiovasc Diabetol. 2022;21(1):226. doi: 10.1186/s12933-022-01664-9.
19. Bilgin S, Kurtkulagi O, Duman TT, et al. Sodium glucose cotransporter-2 inhibitor, Empagliflozin, is associated with significant reduction in weight, body mass index, fasting glucose, and A1c levels in Type 2 diabetic patients with established coronary heart disease: the SUPER GATE study. Ir J Med Sci. 2022;191(4):1647-1652. doi: 10.1007/s11845-021-02761-6.
20. Şahin S, Haliloğlu Ö, Polat Korkmaz Ö, et al. Does treatment with sodium-glucose cotransporter-2 inhibitors have an effect on sleep quality, quality of life, and anxiety levels in people with Type 2 diabetes mellitus?. Turk J Med Sci. 2020;51(2):735-742. doi: 10.3906/sag-2008-37.