ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

ORIGINAL ARTICLE
Endocrinol Res Pract. 2023;27(3):148-153

Leukocyte Telomere Length and Its Association with Serum Silent Information Regulator-1, Body Composition, Glycemic Control, and Diabetic Complications in Type 2 Diabetes Mellitus

ABSTRACT

Objective: The aim of this study is to investigate the length of telomere and serum silent information regulator-1 levels in type 2 diabetic subjects as well as their associations with body composition, glycemic control, and diabetic complications.

Methods: We enrolled 84 type 2 diabetic subjects and 40 controls. The length of telomere and serum silent information regulator-1 (Sirtuin-1) levels, body composition and diabetic complications were examined.

Results: Median T/S ratio tended to be lower in type 2 diabetic subjects compared to the controls (1.03 (0.20-1.48) vs. 1.25 (0.80-1.69), $P = .064$); however, the percentage of having shorter telomere (T/S ratio < 1) was significantly higher in type 2 diabetic subjects than in the controls (47.6% vs. 27.5%, $P = .035$). Serum Sirtuin-1 level was lower in type 2 diabetic subjects than in controls (95.48 ± 29.9 vs. 138.40 ± 42.66 pg/mL, $P < .001$). There were no differences in the length of telomere and serum sirtuin-1 between the groups divided according to the presence of diabetic complications ($P > .05$). The percentage of having shorter telomere was higher in obese patients than in non-obese patients with DM (35.7% vs. 60%, $P = .029$). The T/S ratio was correlated with truncal fat in type 2 diabetic subjects ($r = -0.250$, $P = .028$).

Conclusions: The length of telomere and silent information regulator-1 may have a role in cellular aging in type 2 diabetic subjects in relation to visceral obesity.

Keywords: Telomere length, sirtuin-1, type 2 diabetes mellitus, bioelectrical impedance and obesity

Introduction

The aging process and diabetes mellitus (DM) are closely connected with each other. First, the frequency of DM increases with age. Second, the severity and frequency of aging-related events such as atherosclerosis and cognitive dysfunction are increased in diabetic subjects, and cardiovascular diseases develop earlier.[1] Several factors have been described for cell aging. Telomere is one of them and has been defined as a structure at the end of the chromosome that is involved in ensuring chromosome stability and integrity.[2]

Telomere, which consists of repetitive 5′-TTAGGG-3′ nucleotide sequences and associated proteins, is located in the chromosomal deoxyribonucleic acid (DNA) end portion and protects the chromosome from degradation and damage.[3] Telomere is essential for DNA replication and shortens with each replication cycle.[3] The aging process and the affecting factors have attracted more attention recently. In a limited number of studiestelomere length has been investigated, and telomere shortening has been found in diabetic individuals compared to non-diabetic ones.[4] On the other hand, it has been shown that the telomere length in healthy individuals is not different from patients with a short DM duration.[5] These contradictory results indicate that additional studies are needed on this issue.

Available data suggest a possible relationship between diabetic complications and the length of the telomere. Some studies have indicated a possible connection between the telomere shortening and the risk of DM-related complications.[6] Shorter length of telomere has been detected in type 2 diabetic subjects having microalbuminuria.[7] The length of telomere may also be related to the risk of macrovascular complications such as cardiovascular events in type 2 diabetic subjects.[8] A study has shown that the length of telomere is shortened in

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Received: January 1, 2023
Revision Requested: January 30, 2023
Last Revision Received: March 25, 2023
Accepted: March 30, 2023
Publication Date: July 4, 2023

Cite this article as: Ünver NG, Eroğlu Altınova A, Coşkun M, et al. Leukocyte telomere length and its association with serum silent information regulator, body composition, glycemic control, and diabetic complications in type 2 diabetes mellitus. *Endocrinol Res Pract.* 2023;27(3):148-153.

DOI: 10.5152/erp.2023.22199

diabetic patients with atherosclerotic plaque detected on carotid artery ultrasonography[9] or with a previous myocardial infarction.[10]

Decreased activity of silent information regulator-1 (sirtuin-1) has been demonstrated to have a role in the development of metabolic syndrome and DM.[11] In addition, sirtuin-1 has been proposed as the promoter of longevity due to its association with cellular aging.[12]

In the present study, we planned to examine the length of telomere and serum sirtuin-1 levels in type 2 diabetic subjects and controls. The relations of the length of telomere and sirtuin-1 with glycemic control, diabetic complications, and body composition were determined.

Material and Methods

This study was planned as a single-center, cross-sectional, case-control study. The study's sample size was determined by evaluating similar studies in the literature. Eighty-four eligible type 2 diabetic subjects (46 women and 38 men) aged between 40 and 65 years from the outpatient DM clinic applied in our university hospital between February 2020 and August 2020 and 40 healthy controls (23 women and 17 men) aged between 40 and 65 years were recruited in the study. This age range was selected to lower the possible impact of age on the length of telomere. Patients with any chronic disease or infection and malignancy were excluded. Pregnant women were not included in the study. The medical history and medications of the patients were noted, and physical examination and anthropometric measurements were made. There were 33 (39.3%) patients who have at least one of the diabetic microvascular complications. There was peripheral neuropathy in 24 patients, nephropathy in 16 patients (14 with microalbuminuria, 2 with macroalbuminuria), and retinopathy in 6 patients (all non-proliferative). Seventeen (20.2%) patients had at least one of the macrovascular complications. Healthy control subjects consisted of those who did not have any known systemic diseases and who applied to the outpatient clinics for reasons other than DM with no pathology in the evaluation. The control group was selected from healthy individuals with normal fasting glucose and non-diabetic first-degree relatives.

Fasting blood glucose (FBG), lipids, creatinine, alanine aminotransferase (ALT), and albumin levels were measured after at least 8 hours of fasting in all groups. In the patient group, HbA1c levels were determined.

The relative length of telomere was measured using quantitative polymerase chain reaction (qPCR) method in peripheral blood leukocytes collected from all patients and controls. Deoxyribonucleic acid was extracted from peripheral whole blood using a kit, Vivantis GF-1 Blood DNA Extraction Kit (Vivantis, Malaysia). ScienCell's Relative Human Telomere Length Quantification qPCR Assay Kit (Sciencell, USA) was used for the length of telomere measurement. The telomere primer set recognizes and amplifies telomere sequences. The length of the telomere was expressed as a relative T/S ratio, calculated as the ratio of telomere repeats copy number (Tel) to single gene copy reference for each sample using a formula of $2^{\Delta Ct(sample)}/2^{\Delta Ct(calibrator)} = 2^{-\Delta\Delta Ct}$.[13] We designated the control group as the calibrator, and the relative telomere length of each sample was determined accordingly and we considered T/S ratio <1 as having telomere shortening according to the previous studies.[14]

Silent information regulator-1 levels were studied in 44 patients and 40 controls. Samples were centrifuged to measure serum sirtuin-1 levels and stored at −80°C. Human sirtuin-1 ELISA KIT (Mybiosource, San Diego, California, USA) was used for the measurement of sirtuin-1.

Bioelectrical impedance analysis (BIA) was used to evaluate body composition with the help of alternating current. It has been preferred because of its easy, fast, low cost, and simple use that does not require expertise. Data for total fat % and mass and truncal fat % and mass were recorded. Tanita ViScan AB-140M was used for the measurement of visceral fat ranging from 1 to 59 in arbitrary units.

This study was approved by Ethics Committee of Gazi University on 27.01.2020 with protocol number 109. All subjects gave informed consent.

Statistical Analysis

All analyses were performed using Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA). The normality of the data was determined with the Kolmogorov–Smirnov test. Parametric data were expressed as mean ± standard deviation and non-parametric data as median (minimum-maximum or 25%-75%). Categorical variables were expressed as numbers and percentages. Student's *t*-test or Mann–Whitney *U* test was used for the non-categorical data comparisons. Pearson or Spearman correlation test was used for correlation analyses. χ^2 and Fisher's exact tests were used for the comparison of categorical data. A *P*-value <.05 was considered to be statistically significant. Post hoc power analysis of the study was done with the G*Power3.1 program. Based on the T/S ratio (T/S< 1) in the patient and control groups with a margin of error was 0.05 and a sample size of $n_1 = 82$ and $n_2 = 40$, the power of the study was found to be 0.59. Based on the sirtuin value in the patient and control groups with a margin of error of 0.05, a sample size of $n_1 = 48$ and $n_2 = 40$, and an effect size of 1.16, the power of the study was found to be 0.99.

Results

Eighty-four type 2 diabetic subjects and 40 healthy controls were included in the study. As shown in Table 1, median ages were 55.5 (40-65) years in the patient group and 51.0 (41-65) years in the control group. There were 38 men (45.2%) and 46 women (54.8%) in the patient group and 17 men (42.5%) and 23 women (57.5%) in the control group. Median body mass indices (BMIs) were 29.95 (20-40) kg/m^2 for the patient group and 27.55 (19.6-42.5) kg/m^2 for the control group (*P* = .077). Median DM duration was 8 (0-30) years, and 41 (46.4%) patients had diabetic complications. While 7 patients (8.3%) were newly diagnosed with DM and untreated, 50 (59.5%) patients were treated with oral antidiabetics (OAD), 24 (28.6%) with OAD plus insulin, and 3 (3%) patients with only insulin. The median HbA1c of the patients was 6.9% (5.5-15.9). Forty subjects (47.6%) in the patient group had a diagnosis of concomitant hypertension. Thirteen (13.5%) patients were using acetylsalicylic acid, 8 (8.5%) patients were beta-blockers, and 34 (40.5%) patients were statins.

MAIN POINTS

- The length of telomere was found to be shorter in obese type 2 diabetic subjects.
- Serum silent information regulator-1 level was lower in type 2 diabetic subjects compared to nondiabetic controls
- Increased visceral obesity may affect the telomere length in type 2 Diabetic patient's

Table 1. Demographic and Laboratory Data of the Patients with Type 2 Diabetes Mellitus and Controls

	Patients (n: 84)	Controls (n: 40)	*P*
Age, year (min-max)	55 (40-65)	51 (41-65)	.057[a]
Gender (F/M) (%)	54.8/45.2	57.5/42.5	.775[b]
BMI (kg/m^2)	29.95 (20-40)	27.55 (19.6-42.5)	.077[a]
DM complications, n (%)	41 (48.8)	—	—
Retinopathy, n (%)	6 (7.1)	—	—
Nephropathy, n (%)	16 (19)	—	—
Neuropathy, n (%)	24 (28.5)	—	—
Coronary artery d, n (%)	16 (19)	—	—
Cerebrovascular d, n (%)	1 (1.1)	—	—
HbA1c (%)	6.9 (5.5-15.9)	—	—
Fasting blood glucose (mg/dL)	132.5 (85-404)	95 (77-99)	**<.001**[a]
Total cholesterol (mg/dL)	196.5 (114-323)	230.5 (138-329)	.075[a]
LDL cholesterol (mg/dL)	125.33±38.9	141.88±42.02	**.039**[c]
HDL cholesterol (mg/dL)	46.5 (28-97)	56 (32-91)	**.001**[a]
Triglycerides (mg/dL)	155 (59-632)	110.5 (40-485)	**<.001**[a]
ALT (U/L)	21 (7-80)	22 (8-69)	.273[a]
Albumin (g/dL)	4.3 (4-5)	4.4 (4-4.8)	.332[a]
Creatinine (mg/dL)	0.7 (0.5-1.4)	0.65 (0.5-1.0)	.222[a]
Total fat mass (kg)	24.8 (5.6-47)	23.3 (10.3-46.5)	.446[a]
Total fat %	31.83 ± 9.14	31.72 ± 8.63	.931[a]
Truncal fat mass (kg)	13.79 ± 4.78	12.85 ± 5.42	.335[c]
Truncal fat %	30.64 ± 7,8	29.79 ± 8.37	.539[c]
Visceral fat a.u.	14.06 ± 4.76	11.4 ± 6.03	**.018**[c]
Sirtuin-1 (pg/mL)	95.48 ± 29.95	138.40 ± 42.66	**<.001**[c]
T/S ratio (25%-75%)	1.03 (0.20-1.48)	1.25 (0.80-1.69)	.064[a]
T/S < 1 (%)	47.6	27.5	**.035**[b]

Median (min-max) or Mean (±standard deviation).
ALT, Alanine aminotransferase; BMI, Body mass index; DM, diabetes mellitus; d, disease.
[a]Mann–Whitney *U* test; [b]chi-square test; [c]student's *t*-test.

Twelve (14.3%) patients and 5 (12.5%) subjects in the control group were smokers ($P > .05$).

The median T/S ratio of patients tended to be lower than controls while the difference was not significant (1.03 (0.20-1.48) vs. 1.25 (0.80-1.69), $P = .064$) while the percentage of having telomere shortening (T/S ratio < 1) between the patients and controls (47.6% vs. 27.5%, $P = .035$) was significantly different. T/S ratio results were similar for gender and smoking status ($P > .05$). The T/S ratio and the telomere shortening in the patient group did not show any difference according to the different treatment regimens ($P > .05$).

Mean sirtuin-1 levels were lower in patients than in controls (95.4 ± 29.9 vs. 138.4 ± 42.6 pg/mL, $P < .001$). No difference was observed between females and males as well as smokers and non-smokers in the levels of sirtuin-1 ($P > .05$). Also, sirtuin-1 levels did not show any difference according to the different treatment regimens in DM group ($P > .05$).

No difference was found for the median T/S ratio, the percentage of telomere shortening and mean sirtuin-1 levels between groups divided according to the presence of diabetic chronic complications ($P > .05$) (Table 2). Although the T/S ratio was similar between obese and non-obese diabetic patients ($P = .098$), obese diabetic patients with shorter lengths of telomere were significantly higher than non-obese ones (60% vs. 35%), ($P = .029$).

In the patient group, the T/S ratio did not correlate with age, DM duration, and sirtuin-1 levels ($P > .05$), whereas significant negative correlations were detected between T/S ratio and weight ($r = -0.248$, $P = .025$) and truncal fat ($r = -0.250$, $P = .028$). Sirtuin-1 was correlated positively with fasting blood glucose ($r = 0.334$, $P = .020$). In the control group, there was a significant negative correlation between T/S ratio and sirtuin-1 levels ($r = -0.368$, $P = .019$) (Table 3).

In the patient group, regression analysis was used to identify variables affecting telomere shortening (T/S ratio <1) and sirtuin-1 level. The effects of age, BMI, diabetes duration, fasting glucose, and T/S ratio variables on sirtuin-1 were evaluated by linear regression

Table 2. Demographic and Laboratory Data of the Patients With and Without Diabetic Complications

	Patients With Complications	Patients Without Complications	*P*
Age, year (min-max)	55 (40-65)	56 (41-65)	.710[a]
Gender (F/M) (%)	53.7/46.3	55.8/44.2	.844[b]
BMI (kg/m^2)	30.0 (20-40)	29.9 (21.2-37.4)	.681[a]
Diabetes duration (year)	9 (0-30)	6 (0-22)	.192[a]
HbA1c (%)	7.6 (5.7-15.9)	6.6 (5.5-11.5)	**.004**[a]
Fasting blood sugar (mg/dL)	140 (92-404)	123 (85-270)	**.024**[a]
Total cholesterol (mg/dL)	192 (114-310)	206 (141-323)	.436[a]
LDL cholesterol (mg/dL)	120.05 ± 40.40	130.37 ± 37.17	.227[c]
HDL cholesterol (mg/dL)	46 (32-97)	47 (28-88)	.723[a]
Triglycerides (mg/dL)	154 (59-485)	156 (69-632)	.613[a]
Creatinine (mg/dL)	0.8 (0.6-1.4)	0.7 (0.5-1.2)	.635[a]
Sirtuin-1 (pg/mL)	89.20 ± 22.77	104.28 ± 36.64	.114[c]
T/S ratio (25%-75%)	0.96 (0.18-1.44)	1.12 (0.22-1.78)	.390[a]
T/S < 1 (%)	50.0	45.2	.668[b]

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Mann–Whitney *U* test; [b]chi-square test; [c]Student's *t*-test.

Table 3. Correlation Results for T/S Ratio and Sirtuin-1 in Patients with Diabetes Mellitus

	Patient Group				Control Group			
	T/S ratio		Sirtuin-1		T/S ratio		Sirtuin-1	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	−0.185	.096	−0.017	.907	0.131	.419	0.034	.833
Diabetes duration	0.006	.956	0.132	.372				
Body weight	**−0.248**	**.025**	−0.149	.313	−0.020	.900	0.162	.318
BMI	−0.208	.061	−0.107	.468	−0.132	.416	0.077	.638
HbA1c	−0.094	.403	0.237	.105				
FBG	−0.089	.427	**0.334**	**.020**	0.302	.058	0.116	.474
Total cholesterol	0.048	.666	0.208	.157	−0.030	.861	−0.143	.404
LDL cholesterol	0.050	.654	0.091	.537	0.004	.979	−0.140	.388
HDL cholesterol	−0.073	.512	0.136	.357	−0.012	.943	−0.140	.410
Triglycerides	0.131	.240	−0.069	.639	0.124	.457	0.174	.660
Total fat mass	−0.205	.073	−0.068	.695	−0.070	.667	0.037	.821
Total fat %	−0.139	.229	0.019	.898	−0.066	.685	−0.044	.789
Truncal fat mass	**−0.250**	**.028**	−0.067	.650	−0.063	.701	0.092	.572
Truncal fat %	−0.212	.064	−0.036	.808	−0.050	.757	0.056	.730
Visceral fat a.u.	−0.216	.315	−0.013	.928	−0.083	.613	0.189	.242
Sirtuin-1	0.100	.507	—	—	**−0.368**	**.019**	—	—
T/S ratio	—	—	0.100	.507	—	—	**−0.368**	**.019**

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

analysis, and no related factor was found. Logistic regression analysis including age, BMI, diabetes duration, truncal fat, and sirtuin-1 variables as independent variables showed that BMI was independently a negative risk marker for telomere shortening in patients with type 2 diabetes ($P = .022$).

Discussion

Type 2 diabetic patients have a shorter telomere length than healthy subjects in the present study. Although some studies found that type 2 DM is associated with a shorter length of telomere,[15] there are also reports with controversial results. A previous study suggested that the length of telomere is not changed in type 2 diabetic subjects shortly after diagnosis.[16] Also, Testa et al did not find any difference in the length of telomere between type 2 diabetic subjects who have no diabetic complications and controls.[6] Increased oxidative DNA damage as a result of oxidative stress has been claimed as a reason for shorter monocyte telomere in type 2 diabetic subjects.[17] Supporting this, oxidative stress is negatively associated with T/S ratio in both type 1 and type 2 diabetic subjects.[18] On the other hand, the contributory role of insulin resistance to the telomere shortening has not been clarified yet. A recent study found the shorter length of telomere also in type 1 DM.[19]

There was no association between the length of telomere, FBG, and HbA1c. Regarding the effect of chronic hyperglycemia on telomere shortening, a previous study reported that reasonable glucose concentrations may slow the telomere shortening.[20] On the other hand, another study showed no correlation between the length of telomere and FBG or HbA1c in type 2 diabetic subjects in the beginning date of their 10-year prospective study.[8] Salpea et al[21] also did not observe this kind of association in their study. In the study of Ma et al[18] covering both type 1 and type 2 diabetic subjects, an association was found between the length of telomere, FBG, and HbA1c in the correlation analysis performed with all participants, but there was no separate data in terms of the correlation analysis performed in type 2 diabetic subjects. Therefore, divergent results obtained from the studies indicate that the relationship between the length of telomere and the parameters of glycemic control needs further investigation.

In our study, serum sirtuin-1 levels were lower in the diabetic group than controls. There are a few controversial data regarding the circulating sirtuin-1 levels in type 2 diabetic subjects. There are some studies reporting decreased serum sirtuin-1 levels in type 2 DM,[22] whereas increased sirtuin-1 levels were also reported.[23] The association of the length of telomere with sirtuin-1 is not known exactly. Sirtuin-1 was a positive regulator of the length of telomere in a previous mice study.[24] In contrast, no relationship was also reported between the length of telomere and expression of sirtuin-1 in the circulating leukocytes from the patients with coronary artery disease.[25] The length of telomere did not correlate with sirtuin-1 levels in the patient group, whereas a negative correlation was found between them in the control group in our study. These unexpected results might be related to complex metabolic pathways seen in DM or varied treatment modalities in our patients. Besides, different measurement methods of sirtuin-1 such as in the circulation or in the leukocytes may produce different results. In support of this, it has been reported that leukocyte sirtuin-1 expression was reduced, whereas similar serum sirtuin-1 levels were found between patients with type 1 DM and controls.[19]

T/S ratio and T/S <1 percentage were similar in the patient group according to the presence of diabetic complications. Also, there was no decreasing trend in T/S ratio and T/S < 1 percentage with an increasing number of complications. In accordance with our result, Olivieri et al[10] reported no relationship between concomitant nephropathy or retinopathy and the length of telomere in type 2 diabetic subjects. Januszewski et al[26] also found no association between the presence of complications and the length of telomere in type 1 DM. Contrary to these reports, Testa et al[6] observed that the length of telomere became shorter with the increasing number

of complications in type 2 diabetic subjects. Therefore, the possible association between the length of telomere and diabetic complications merits further research.

No correlation of DM duration was found with the length of telomere in our study. Murillo-Ortiz et al[5] evaluated type 2 diabetic subjects by grouping them as those with a duration of 10 years or more and those with a duration of less than 1 year and they reported significant telomere shortening in the longer DM duration group. However, some studies revealed that there is no such relationship, similar to our data.[17] In this regard, it can be thought that DM duration does not fully reflect the severity of the disease.

There is a strong evidence that obesity has a negative impact on the telomere shortening.[27] The percentage of shorter length of telomere was higher in our obese diabetic patients than non-obese diabetic ones, which is one of the important results of our study. Moreover, we found that T/S ratio was significantly correlated with truncal fat mass in a negative manner, indicating the importance of visceral obesity on the aging process in type 2 diabetic subjects. Ma et al[18] reported that the length of the telomere did not correlate with waist-to-hip ratio (WHR) in type 2 DM; however, there was no body composition measurement. Studies on the association of the length of telomere with body fat composition in DM are very limited in the literature. A previous study including BIA measurement found that the length of telomere shortens as visceral fat increases in type 2 diabetic subjects, but not in all ethnic groups.[28] Taken together, the connection between the length of telomere and excess visceral fat in type 2 diabetic subjects is important but somewhat complex and there are unanswered questions.

As a limitation of our study, we measured the length of the telomere, not adipocyte telomere length. One can speculate that the length of telomere measurement from circulating leukocytes may not fully reflect the telomere shortening of adipose tissue in obesity. Regarding this, the length of telomere in the leukocytes has been revealed to be strongly correlated with the length of telomere in the adipose tissue of severely obese subjects,[29] which supports the reliability of the length of telomere measurement in relation to obesity. Second, it can be questioned that the antidiabetic treatments which patients use may affect the length of telomere measurements. Regarding this subject, treatment with acarbose has unfavorable effect on the length of telomere in type 2 diabetic subjects,[30] but there was no patient taking this drug in our diabetic group. Lastly, our *r*-values in the correlation analysis seem relatively small. The reason may be associated with the presence of multiple confounding metabolic factors which may affect the relationships between the variables. However, regarding the clinical significance, our results are quite reliable since the *P* values for T/S ratio and sirtuin-1 were markedly lower.

Conclusion

This is the first study examining the telomere length a marker of aging at the cellular level, and sirtuin-1 as an anti-aging molecule in type 2 diabetic subjects. We demonstrated the telomere shortening and low serum sirtuin-1 levels in type 2 DM. Moreover, we found an unfavorable effect of visceral obesity on the telomere shortening in diabetic subjects.

Ethics Committee Approval: This study was approved by Ethics Committee of Gazi University (Date: 27.01.2020, Approval No: 109).

Informed Consent: Written informed consent was obtained from the patients/patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.G.Ü., A.E.A.; Design – N.G.Ü., M.C.; Supervision – F.B.T., M.A.; Resources – N.G.Ü., M.M.Y.; Materials – N.G.Ü., A.E.A.; Data Collection and/or Processing – M.C., N.G.Ü.; Analysis and/or Interpretation – M.M.Y., N.G.Ü.; Literature Search – A.E.A., N.G.Ü.; Writing – N.G.Ü., A.E.A., M.C.; Critical Review – İ.Y., M.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

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