ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Relationships Between Chocolate Consumption and Endothelial Dysfunction in Patients with Heart Failure

Kalp Yetmezliği Hastalarında Çikolata Tüketimi ile Endotel Disfonksiyonu Arasındaki İlişkinin Belirlenmesi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: Dietary recommendations, in addition to medications, have recently become important in the treatment of heart failure. Our study aimed to show the positive effects of both milk chocolate and dark chocolate on heart failure through endothelial functions.

Methods: Twenty patients with heart failure and reduced ejection fraction were included in the study. In this randomized, crossover study, some of the patients consumed milk chocolate and some consumed dark chocolate. We recorded the patients' 6-minute walking tests, flow-mediated dilatation values, plasma catechin, epicatechin, and N-terminal pro-brain natriuretic peptide values before and after chocolate consumption. After 2 weeks, their chocolate consumption was changed. The same parameters were measured again.

Results: A significant decrease was observed in N-terminal pro-brain natriuretic peptide values after consumption of both milk chocolate (356 ± 54.2 and 310 ± 72.1 pg/mL; $P = .007$) and dark chocolate (341 ± 57 and 301 ± 60.1 pg/mL;$P = .028$). Flow-mediated dilation values increased after dark chocolate consumption (8.9 ± 3% and 14 ± 4.5%; $P = .019$).

Conclusion: Chocolate consumption acutely decreases N-terminal pro-brain natriuretic peptide values in heart failure. Dark chocolate consumption also seems to improve endothelial functions by increasing flow-mediated dilation values.

Keywords: Heart failure, chocolate, flow-mediated dilation

ÖZET

Amaç: Son zamanlarda kalp yetmezliği tedavisinde ilaçlara ek olarak diyet önerileri de önem kazanmıştır. Bu çalışmanın amacı; hem sütlü çikolatanın, hem de bitter çikolatanın kalp yetersizliği üzerindeki olumlu etkilerini endotel fonksiyonları üzerinden göstermektir.

Yöntemler: Çalışmaya düşük ejeksiyon fraksiyonlu kalp yetmezliği tanısı ile takip edilen yirmi hasta dahil edildi. Randomize cross-over olarak tasarlanan çalışmada hastaların bir kısmı sütlü, bir kısmı da bitter çikolata tüketti. Hastaların çikolata tüketimi öncesi ve sonrası 6 dakikalık yürüme testi sonuçları, akım aracılı dilatasyon değerleri, plazma kateşin, epikateşin ve NT pro BNP değerleri kaydedildi. İki hafta sonra hastaların tükettikleri çikolata tipleri değiştirildi. Aynı parametreler tekrar ölçüldü.

Bulgular: Hem sütlü çikolata (356 ± 54,2, 310 ± 72,1 pg/mL; $P = ,007$) hem de bitter çikolata (341 ± 57,301 ± 60,1 pg/mL; $P = ,028$) tüketiminden sonra NT pro BNP değerlerinde anlamlı bir düşüş gözlendi. Bitter çikolata tüketiminden sonra FMD değerlerinde anlamlı artış izlendi (%8,9 ± 3, %14 ± 4,5; $P = ,019$).

Sonuç: Çikolata tüketimi kalp yetersizliğinde NT proBNP değerlerini anlamlı bir şekilde düşürmektedir. Bitter çikolata tüketimi de kalp yetersizliği hastalarında FMD değerlerini artırarak endotel fonksiyonlarını iyileştiriyor gibi görünmektedir.

Anahtar Kelimeler: Kalp yetersizliği, çikolata, akım aracılı dilatasyon

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Received: October 27, 2021
Accepted: March 16, 2022

Cite this article as: Dural İE, Onrat E, Çelik S, et al. The relationships between chocolate consumption and endothelial dysfunction in patients with heart failure. *Turk Kardiyol Dern Ars.* 2022;50(5):334-339.

DOI:10.5543/tkda.2022.21249

The benefits of chocolate in cardiovascular diseases have been demonstrated in many studies.[1] This benefit is thought to be due to flavonols, one of the components of cocoa. Flavonols are composed of epicatechin and catechin monomers.[2] Catechin and epicatechin decrease oxidative stress on the endothelium by increasing nitric oxide release. They also cause vasodilation as an acute effect. Vasodilation and improvement of endothelial function are the targets of many drugs in treating both atherosclerotic heart disease and heart failure.[3]

Heart failure is a global health problem because it has high mortality and morbidity and high hospitalization rates.[4] Endothelial dysfunction is almost always present in heart failure, the most unintended consequence of heart disease. Endothelial dysfunction is associated with poor prognosis in heart failure by increasing the workload of the heart.[5] Therefore, vasodilation is an important part of the treatment of heart failure. Angiotensin-converting enzyme (ACE) inhibitors and neprilysin inhibitors mainly target arterial vasodilation.[6]

One of the non-invasive tests that show endothelial functions is flow-mediated dilation (FMD).[7] Flow-mediated dilation is decreased in coronary artery disease, peripheral artery disease, and heart failure. Impaired FMD values are also associated with mortality and cardiovascular disease.[8] Flow-mediated dilation decreases in heart failure due to endothelial dysfunction resulting from the activation of the sympathetic system, disruption of the renin–angiotensin–aldosterone system, and increase in inflammatory molecules.[9] The increase in FMD has been the subject of study to optimize non-drug therapies such as cardiac resynchronization therapy and cardiac rehabilitation.[10] Flow-mediated dilation has also been used as an important factor in investigating the cardiovascular benefits of foods (olive oil, curcumin, chocolate).[11-13]

Chocolate-rich flavonols have been shown to increase FMD and N-terminal pro-brain natriuretic peptide (NT proBNP) levels for chronic use in patients with heart failure. N-terminal pro-brain natriuretic peptide levels are known as a deterministic factor for the prognosis of heart failure.[14] In our study, we tried to evaluate the acute effect of dark chocolate rich in flavonol and milk chocolate with low flavonol levels in heart failure through catechin and epicatechin levels. Also, we evaluated the acute effect of both chocolates with NT proBNP and FMD.

Methods

Our study has a randomized crossover design. We recruited 20 patients with heart failure and divided them into 2 groups. Randomly, one group consumed dark chocolate; the other group consumed chocolate with milk.

After a 2-week washout, the chocolate consumptions were reversed. Exclusion criteria were as follows: New York Heart Association (NYHA) class 3-4 heart failure, acute coronary syndrome, diabetes mellitus (DM), severe kidney failure, severe liver failure, malignancy, and chocolate allergy (Figure 1).

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
DM	Diabetes mellitus
FMD	Flow-mediated dilation
NT-ProBNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA	New York Heart Association

Written informed consent was obtained from each participant, and the Ethics Committee of Afyon Kocatepe University School of Medicine approved the study. (Date:May 4, 2018, No: 2018/136-).

Patients

Twenty patients who had been followed up for at least 1 year between June 6, 2017, and February 2, 2022 at Afyonkarahisar Health Sciences University Hospital with NYHA class 1-2 heart failure with reduced ejection fraction (EF $\leq$ 40) were included in the study.

Study Chocolates

Milk chocolate with 29% cocoa and dark chocolate with 80% cocoa were used as study chocolates. The contents are shown in Table 1.

Flow-Mediated Dilation

Flow-mediated dilation was obtained from the right brachial artery by ultrasonographic methods using methodological and technical guidelines.[15] Pre-chocolate measurements were taken after 6 hours of fasting. The use of caffeine and alcohol was discontinued 24 hours before the procedure. The patients continued to use beta-blockers, ACE inhibitors, and mineralocorticoid receptor antagonists. None of the patients used nitrates. The patients were kept supine for 20 minutes in a quiet, dusk room, and the procedure was initiated.

An Aplio MX duplex Doppler ultrasound device (Toshiba, Japan, 2010) and a 7.5 MHz probe were used to measure brachial FMD. In the supine position, the basal measurements of the right brachial artery were longitudinally recorded in the end-diastole, approximately 5 cm proximally to the antecubital fossa, and the cuff was placed in the proximal portion of the brachial artery. The Doppler probe was inflated until no blood flow from the brachial artery was detected and held at this pressure for 5 minutes. The cuff was then deflated, and the arterial diameter was measured 45-60 seconds after the cuff was released. Flow-mediated dilation, showing the brachial artery vasodilator response to reactive hyperemia, was calculated as the maximum percentage change in the internal diameter of the brachial artery after basal and reactive hyperemia [FMD (%) = (maximum diameter – diameter at rest) × 100/(diameter at rest)].[16]

6 Minutes Walking Test

After the FMD measurements, the patients walked in a straight, quiet corridor at the highest possible speed under the supervision of a physician for 6 minutes. Before and after walking, blood pressure, heart rate, and saturation measurements with pulse oximetry were measured. In addition, the distance they walked for 6 minutes was recorded.

Biochemical Measurements

Human NT-ProBNP levels were determined using an enzyme-linked immunosorbent assay kit (USCN, Wuhan, China) as per the manufacturer's recommendations, and absorbance was measured at 450 nm using a spectrophotometer (Multiskan FC Microplate, Thermo Fisher Scientific Instruments Co. Ltd., Shanghai, China). Results are given in pg/mL. In addition, serum catechin and epicatechin levels were studied by high-performance liquid chromatography technique on a C-18 column (250 × 4.6 mm, 5 μm; Phenomenex, Torrance, CA, USA) and

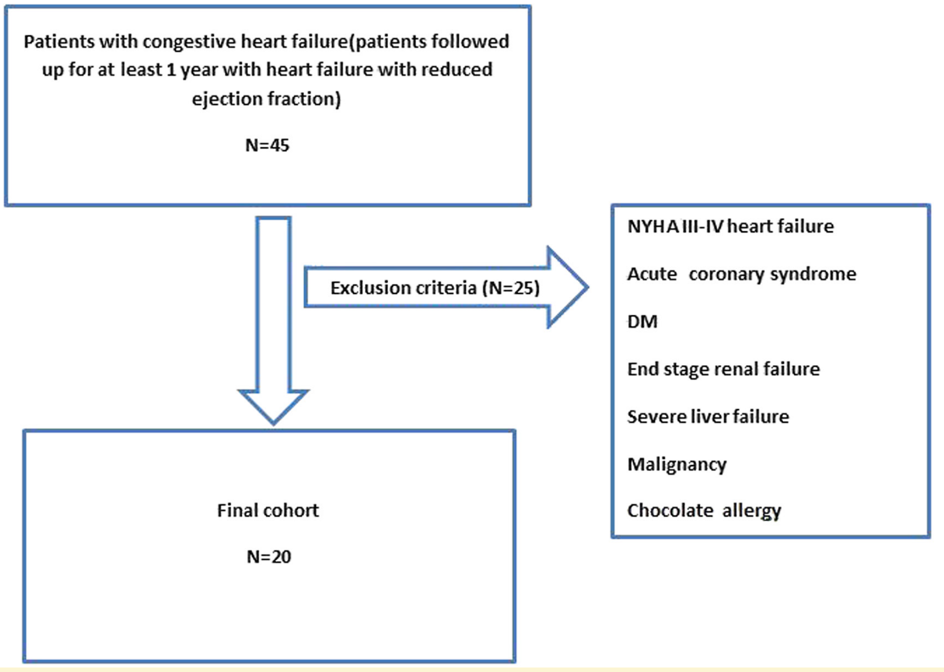

Figure 1. Inclusion–exclusion criteria of the study. ACE, Angiotensin converting; DM, Diabetes mellitus; EF, Ejection fraction; FMD, Flow-mediated dilation; NT proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

a Thermo Scientific Ultimate 3000 (Thermo Fisher Scientific, Waltham, Mass, USA) using an ultraviolet detector (280 nm). Results are given for catechin and epicatechin levels in ng/mL.

Statistical Analysis

The data were evaluated using the SPSS version 20.0 (IBM Corp., Armonk, NY, USA). A preliminary power analysis was based on the results of previous studies.[17] For a significance level of 5%, 10 patients per treatment group were assumed to be needed to reach a statistical power of 80%. Normally distributed quantitative data were expressed as mean ± standard deviation and non-normally distributed data as median (25%-75%, interquartile range [IQR]) values. The normal distribution of variables was tested with the Kolmogorov–Smirnov test. Normally distributed variables were evaluated with the *t* test, and non-normally distributed variables were evaluated with the Mann–Whitney *U* test. In the comparison of before and after chocolate

Table 1. Contents of the Study Chocolates

For 100 g	Milk Chocolate	Dark Chocolate
Fat (g)	30	37
Saturated	15	23
Carbohydrate (g)	57	41
Sugar	56	38
Protein (g)	8	7.4
Fiber (g)	2.6	9.5
Cocoa (%)	29	80
Salt (g)	0.05	0.07
Total (g)	60	60

Table 2. Baseline Characteristics of Study Population

Age (years)	58.4 ± 9.2
Female gender	8 (40%)
Ejection fraction (%)	32 (20-38)
Ischemic heart failure	17 (85%)
Heart failure duration (years)	5.8 ± 3.2
Blood pressure (mmHg)	125 ± 9/75.8 ± 9.2
Heart rate (bpm)	63.8 ± 11.4
Creatinine (mg/dL)	1.2 ± 0.4
Glucose (mg/dL)	94.3 ± 9.6
Aspartate transaminase (U/L)	35.6 ± 7.1
Alanine transaminase (U/L)	39.6 ± 8.8
Hemoglobin (g/dL)	11.3 (8.5-15.5)
Comorbidities	
Coronary artery disease	18 (90%)
Hypertension	13 (65%)
Dyslipidemia	14 (70%)
Atrial fibrillation	5 (25%)
Implantable cardioverter defibrillator implantation	7 (35%)
Obesity	6 (30%)
Chronic obstructive pulmonary disease	4 (20%)
Obstructive sleep apnea syndrome	2 (10%)

Table 3. Medications Used by the Patients

Beta-blockers	Metoprolol 200 mg (o.d.)	5 (25%)
	Metoprolol 100 mg (o.d.)	7 (35%)
	Metoprolol 50 mg (o.d.)	1 (5%)
	Carvedilol 25 mg (b.i.d.)	3 (15%)
	Carvedilol 12.5 mg (b.i.d.)	3 (15%)
	Bisoprolol 10 mg (o.d.)	1 (5%)
ACE inhibitors (%)	Ramipril 10 mg (o.d.)	7 (35%)
	Ramipril 5 mg (o.d.)	2 (10%)
	Ramipril 2.5mg (o.d.)	2 (10%)
	Perindopril 10 mg (o.d.)	5 (25%)
	Perindopril 5 mg (o.d.)	1 (5%)
	Trandolapril 0.5 mg (o.d.)	1 (5%)
MRA (%)	Spiranolakton 25 mg	18 (90%)
Digoxin (%)	Digoxin 0.25 mg (o.d.)	4 (20%)
ARNI (%)	Valsartan-sakubitril 97/103 mg	1 (20%)
	Valsartan-sakubitril 49/51 mg	2
ASA (%)	Aspirin 100 mg	15 (75%)
Oral anticoagulants (%)	Apixaban 5 mg (b.i.d.)	2 (10%)
	Rivaroxaban 20 mg (o.d.)	2 (10%)
	Edoxaban (o.d.)	1 (5%)

ACE, angiotensin-converting enzyme; ASA: Acetylsalicylic acid; MRA: Mineralocorticoid receptor antagonist; ARNI: Angiotensin receptor-neprilysin inhibitor; o.d: omne in die (once a day); b.i.d: bis in die (twice a day).

consumption, the paired *t* test was used for normally distributed variables and the Wilcoxon test was used for non-normally distributed variables. The relationship between NTproBNP, catechin and epicatechin was evaluated with the Pearson correlation coefficient. A 2-sided *P*-value <.05 was considered statistically significant.

Results

The demographic characteristics of the patients are given in Table 2. Of the 20 patients who participated in the study, 12 were male and 8 were female, with a mean age of 58.4 ± 9.2 years.

Study parameters before chocolate consumption are given in Table 3. There were no significant differences between milk and dark chocolate groups in any of the variables examined.

Table 4. Study Parameters Before Chocolate Consumption

Parameters	Milk Chocolate	Dark Chocolate	*P*
6 minutes walk (m)	344 ± 96	332 ± 97	.421
Flow-mediated dilation (%)	7.5 ± 3.2	8.9 ± 3	.215
NT pro-BNP (pg/mL)	356 ± 54	341 ± 57	.705
Catechin (ng/mL)	34 ± 8	40 ± 20	.363
Epicatechin (ng/mL)	30 ± 10	23 ± 7	.508

Table 5. Study Parameters Before and After Chocolate Consumption

Parameters	Before Chocolate	After Chocolate	*P*
Milk Chocolate			
6 minutes walking test (m)	344 ± 96	347 ± 101	.501
Flow-mediated dilation (%)	7.5 ± 3.2	8.2 ± 3.6	.314
NT pro-BNP (pg/mL)	356 ± 54.2	310 ± 72.1	.007
Catechin (ng/mL)	34 ± 8.1	85.1 ± 23.3	.004
Epicatechin (ng/mL)	30 ± 9.5	77.2 ± 22.7	.023
Dark Chocolate			
6 minutes walking test (m)	332 ± 97	329 ± 91	.421
Flow-mediated dilation (%)	8.9 ± 3	14 ± 4.5	.019
NT pro-BNP (pg/mL)	341 ± 57	301 ± 60.1	.028
Catechin (ng/mL)	40 ± 20	152 ± 41.3	.006
Epicatechin (ng/mL)	23 ± 7	135 ± 32.4	.005

NT pro-BNP, N-terminal pro-brain natriuretic peptide.

Study parameters after chocolate consumption are given in Table 4. The mean levels of catechin and epicatechin are increased, and NT pro-BNP levels are decreased significantly in both groups. In addition, the mean FMD values are markedly increased after consuming dark chocolate.

The acute effects of milk chocolate and black chocolate are shown in Table 5. Both chocolates significantly decreased the mean level of NT pro-BNP, but no significant difference was observed between the 2 chocolate groups. However, catechin and epicatechin levels were significantly higher after dark chocolate consumption. In addition, the mean Flow-mediated dilation value was also found to be considerably higher after dark chocolate.

The correlation analysis of plasma catechin and epicatechin levels with NT pro-BNP and FMD values is given in Table 6. A negative correlation was found between blood plasma catechin and epicatechin values and NT pro BNP values in both chocolate

Table 6. Comparison of Study Parameters After Chocolate Consumption

Parameters	Milk Chocolate	Dark Chocolate	*P*
6 minutes walking test (m)	347 ± 101	329 ± 91	.285
Flow-mediated dilation (%)	8.2 ± 3.6	14 ± 4.5	.040
NT pro-BNP (pg/mL)	310 ± 72.1	301 ± 60.1	.239
Catechin (ng/mL)	85.1 ± 23.3	152 ± 41.3	.023
Epicatechin (ng/mL)	77.2 ± 22.7	135 ± 32.4	.019

NT pro-BNP, N-terminal pro-brain natriuretic peptide.

Table 7. Correlation Analysis of Catechin and Epicatechin Levels with NT pro-BNP and FMD

Variables	Milk Chocolate		Dark Chocolate	
(*r*)	Catechin	Epicatechin	Catechin	Epicatechin
NT pro-BNP	−0.571	−0.361	−0.659	−0.719
FMD	0.277	0.115	0.078	0.053

NT pro-BNP, N-terminal pro-brain natriuretic peptide; FMD, flow-mediated dilation.

groups (Table 7). However, this correlation is stronger in dark chocolate. There was no significant correlation between FMD values and catechin epicatechin levels.

Discussion

Previous studies have shown that dark chocolate may have positive benefits on heart failure. Due to the catechin and epicatechin in dark chocolate, positive effects were observed in some parameters in heart failure patients by providing vasodilation. This study showed that both dark chocolate and milk chocolate had positive effects on FMD and NT pro-BNP in heart failure.[14] We concluded that dark chocolate has a greater positive effect on endothelial function than milk chocolate in the same patient population. Furthermore, we observed that these positive effects were associated with increased catechin and epicatechin levels in plasma after chocolate consumption.

N-terminal pro-brain natriuretic peptide has prognostic value in heart failure and is frequently used in treatment follow-up. High plasma values are detected in periods when the heart's afterload is increased.[18] It is known that drugs used in heart failure increase afterload and decrease NT pro-BNP levels by decreasing peripheral vascular resistance.[19]

Catechin and epicatechin, which are flavonols in chocolate, provide endothelium-dependent peripheral vasodilation via endothelin-1 and nitric oxide.[20] Chronically, a decrease in NT pro BNP values, which are thought to be due to decreased cardiac afterload due to peripheral vasodilation, was observed in high-dose flavanol consumption.[21]

Our study showed that the acute use of both dark chocolate and milk chocolate significantly decreased NT pro-BNP levels. We found that this decrease was correlated with the increased catechin epicatechin levels in plasma after chocolate consumption. We found this correlation in both chocolate with low and high cocoa groups.

N-terminal pro-brain natriuretic peptide levels are elevated in almost all patients hospitalized with acute heart failure and decrease with effective diuretic and vasodilator therapy.[22,23] Some studies have shown a decrease in natriuretic peptide levels with sodium restricted diets. Therefore, the diets of patients with acute heart failure who are hospitalized include sodium-restricted foods.[24]

However, in general, other foods for acute heart failure are not considered in the hospital diet in routine practice. The acute consumption of chocolate causes a decrease in NT pro-BNP levels and suggests that it may be included in the diet of hospitalized non-diabetic patients with acute heart failure.

Endothelial dysfunction is present in almost all heart failure patients. In the pathophysiology of endothelial dysfunction associated with flow-mediated dilation, there are complex causes of low cardiac output, increased ACE and endothelial activity, cytokine activities, and oxidative stress.[5] As a result of this pathological process in heart failure, endothelial dysfunction develops, and FMD decreases. Peripheral vascular resistance, which increases with endothelial dysfunction, causes worsening in heart failure. Therefore, endothelial function and FMD are independent predictors of both hospitalizations and mortality in heart failure.[9]

That standard treatment of heart failure increases FMD and decreases vascular resistance. Additionally, it is known that exercise and various foods have positive effects on endothelial function. Chocolate consumption has also been shown in some studies to increase FMD.[25]

In our study, we have shown that dark chocolate consumption increases FMD. However, this acute effect was not observed after consuming milk chocolate. This may be due to catechin and epicatechin, which raised more in plasma after dark chocolate consumption. Plasma catechin and epicatechin levels seem to regulate endothelial functions at higher levels.

Limitations

The most important limitation of our study is the small sample size. In addition, we included only patients with reduced ejection fractions in the study. Since we did not include other phenotypes of heart failure, we could not show the effect of chocolate on other phenotypes.

The most important strength of our study is that it was designed as a cross-over study. In this way, we reduced the variability between patients.

Conclusion

Chocolate consumption, especially chocolate containing high cocoa, seems to be beneficial for heart failure by positively affecting endothelial functions.

Visual summary of the article can be seen in Figure 2.

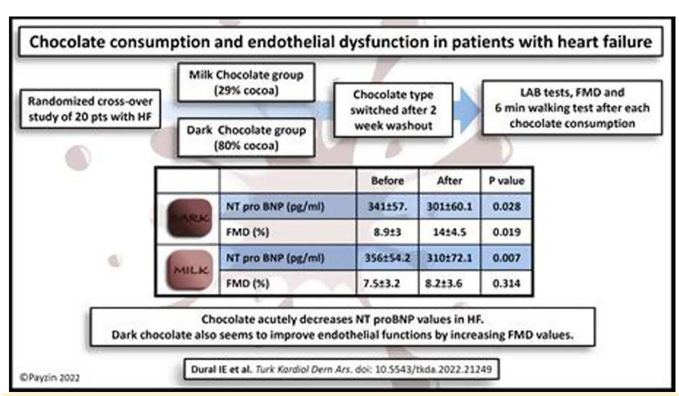

Figure 2. A visual summary of the article.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Afyon Kocatepe University School of Medicine (Approval Date: May 4, 2018; Approval Number: 2018/136-).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – İ.E.D., E.O., S.Ç., A.V., Z.Y.; Design – E.O., S.Ç., A.V., Z.Y.; Supervision – E.O., S.Ç.; Funding – İ.E.D., E.O., S.Ç., A.V., Z.Y.; Materials – S.G, Ç.G, C.K, U.A.; Data Collection and/or Processing – E.O, S.Ç, A.V, Z.Y.; Analysis and/or Interpretation –U.A, Z.Y.; Literature Review – İ.E.D., Z.Y., S.G., Ç.G., C.K., U.A.; Writing – İ.E.D., Z.Y.; Critical Review – İ.E.D., Z.Y.

Declaration of Interests: We have no conflict of interest.

Funding: This study was supported by a grant from the Medical Faculty of Afyonkocatepe University Research Project Commission, project number: 17kariyer194.

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