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Cardiovascular diseases and diabetes mellitus

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ABSTRACT

Cardiovascular diseases are among the leading causes of death worldwide. Atherosclerotic cardiovascular diseases consist of a broad spectrum of diseases such as coronary artery disease, carotid artery disease, peripheral artery diseases, cerebral vascular diseases and visceral artery diseases. Although atherosclerosis occurs over time due to age; hypertension, hyperlipidemia, smoking, and diabetes mellitus are important factors that play a role in the emergence of atherosclerosis. Diabetes mellitus has an active role in the development of atherosclerotic cardiovascular disease. It is expected that there will be a significant increase in the incidence of diabetes-related cardiovascular diseases in the future. In this review, it is aimed to review the coexistence of diabetes with different cardiovascular diseases and its menanisms.

Keywords: Diabetes mellitus, hyperglisemia, heart, vascular disease

Cardiovascular diseases are among the leading causes of death worldwide. More than 30% of deaths worldwide are of cardiovascular origin. The main factor in these deaths is atherosclerosis. Atherosclerotic cardiovascular diseases consist of a broad spectrum of diseases such as coronary artery disease, carotid artery disease, peripheral artery diseases, cerebral vascular diseases and visceral artery diseases [1, 2]. Since atherosclerosis is a systemic disease, it usually affects more than one system. Although atherosclerosis occurs over time due to age, hypertension, hyperlipidemia, smoking, and diabetes mellitus (DM) are important factors that play a role in the emergence of atherosclerosis.

DM has an active role in the development of atherosclerotic cardiovascular disease. It is reported that by 2025, approximately 380 million people worldwide will have type 2 DM [3]. Thus, there will be a significant increase in the incidence of diabetes-related cardiovascular diseases.

In this review, it is aimed to review the coexistence of diabetes with different cardiovascular diseases and its mechanisms.

The Relationship Between Diabetes Mellitus and Vascular Diseases

The relationship between hyperglycemia and vascular diseases has a complex structure. Hyperglycemia causes Nuclear Factor-Kappa B (NF-KB) activation. NF-KB is a key mediator that regulates proinflammatory and proatherosclerotic target genes in endothelium, vascular smooth muscle cells and macrophages. This activation is known to increase oxidative stress. Hyperglycemia also causes a decrease in nitric oxide synthesis in platelets and an increase in free radical formation. In addition, it has been shown in experi-

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mental studies that with an increase in plasminogen activator inhibitor-1 level, it causes a decrease in fibrinolysis, plaque instability and dysfunctional arterial remodeling [2].

Effect of Diabetes Mellitus on Cardiovascular Risk Factors

Dyslipidemia plays an important role in the pathogenesis and progression of cardiovascular diseases. The essential feature of the lipid disorder in patients with DM is the presence of high plasma triglyceride levels, decreased high-density lipoprotein cholesterol (HDL-C) concentration, and increased concentration of small-density low-density lipoprotein cholesterol (LDL-C) particles in patients. This occurs due to increased plasma free fatty acid ratios due to increased insulin resistance [4].

In the presence of adequate glycogen stores in the liver, high free fatty acid values stimulate triglyceride production. Failure to provide "up" regulation of Apolipoprotein A-I (ApoA-I) production due to insulin resistance contributes to the formation of decreased HDL-C levels. Tumor Necrosis Factor-α (TNF-α) plays a role in insulin resistance in obese patients and leads to a decrease in HDL-C. Apart from these, many key enzymes that affect HDL-C metabolism undergo changes in patients with insulin resistance. In some people, insulin resistance results in decreased conversion of lipoprotein lipase to hepatic lipase, which contributes to HDL-C reduction. While

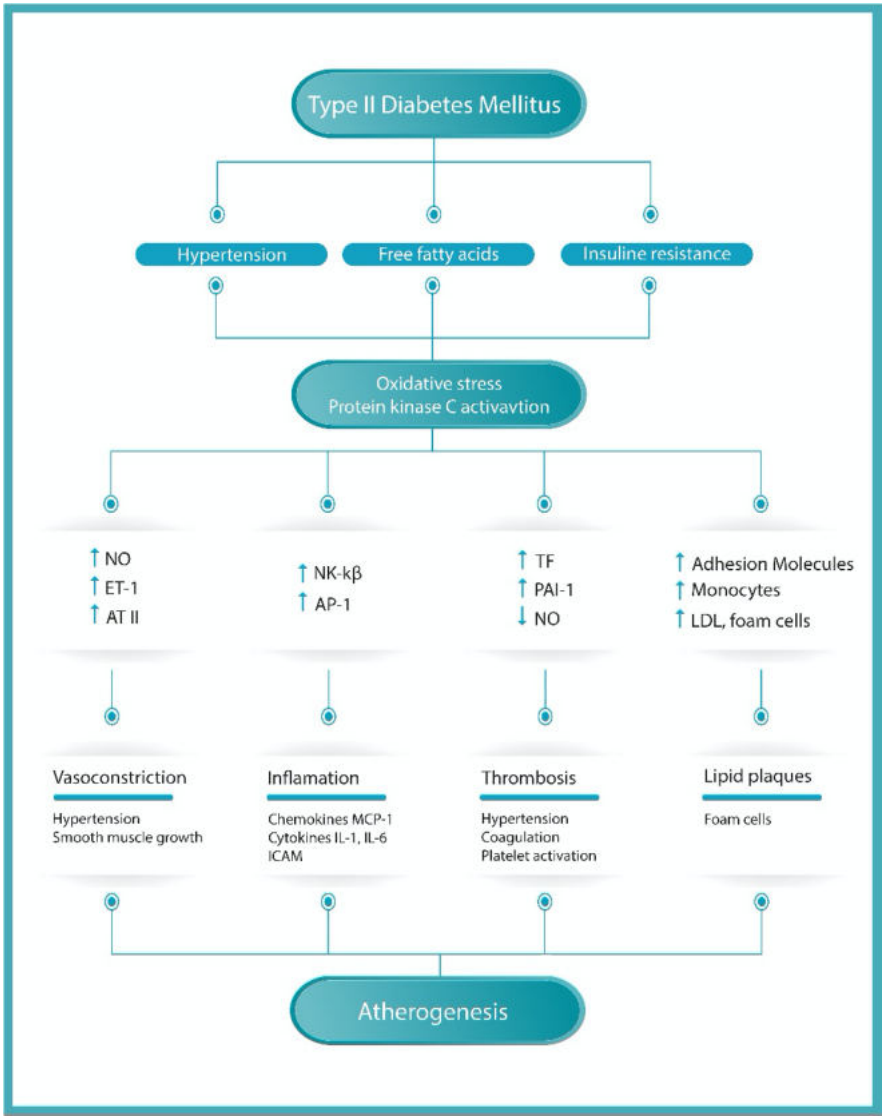

Fig. 1. Pathophysiological mechanisms leading to atherosclerotic vascular disease in Type 2 diabetes mellitus. AP-1 = Activator protein 1, AT II = Angiotensin II, ET-1 =: Endothelin-1, ICAM = Intercellular adhesion molecule, MCP = Monocyte chemoattractant protein, NF-κβ = Nuclear factor-κβ, NO = Nitric oxide, PAI-1 = Plasminogen activator inhibitor-1, TF = Tissue factor.

insulin resistance does not cause an increase or no change in cholesterol esterification provided by cholesterol acyltransferase, it causes an increase in Cholesteryl Ester Transfer Protein (CETP) activity. CETP activity causes a decrease in HDL-C esters [5].

Hypertension is an important risk factor that can develop in patients with DM. The most well-known feature of DM is the deterioration of the autonomic balance in the form of a significant decrease in parasympathetic tone and a relative increase in sympathetic tone. In particular, an increase in sympathetic tone occurs in cerebral centers that provide autonomic control due to high blood sugar [6]. This increase in tone in diabetic patients affects cardiac and vascular functions and leads to hypertension [7]. The mechanism of atherogenesis due to DM is shown in Fig. 1 [8, 9].

Diabetes Mellitus and Coronary Artery Disease

Atherosclerosis, which develops due to diabetes, affects the coronary arteries and leads to the formation of coronary artery disease (CAD). In diabetic patients, atherscleroticprocess progresses, nitric oxide release decreases, inflammation and platelet activation increase, leading to coronary events [10]. In a study in which data were collected from 52 countries, it was revealed that the presence of DM increased the risk of CAD by 10% [11]. In addition, the prevalence of hypertension and hyperlipidemia, which are known as risk factors for CAD, has been reported up to 70% in patients with DM [12]. In the WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE), patients from 10 countries were examined and the prevalence of DM was found to be 31.5% [13].

In addition to causing CAD, diabetes also affects mortality and long-term prognosis after myocardial infarction [14]. In fact, the presence of DM in patients with CAD also affects treatment strategies. Although percutaneous coronary interventions (PCIs) have come to the forefront today, the presence of DM highlights coronary artery bypass grafting (CABG) surgery as a treatment option, especially in multi-vessel patients. In a study conducted in this direction, the results of PCI (n =1.556) and CABG (n =1.281) in patients with DM with impaired left ventricular function were compared. At 5-year follow-up after treatment, major adverse cardiovascular and cerebral event development rates were approximately twice as high in the PCI group [15].

Apart from this, long-term patency after coronary stent procedure in CAD patients is very important in terms of both patient comfort and treatment costs. Mechanisms similar to atherosclerosis play a very important role in the obstruction here. In a study involving 18,910 patients who underwent coronary stenting, they were divided into two groups as those with DM (n =5123) and those without (n =13.787). At the end of the study, the risk of late-stage stent thrombosis was found to be significantly higher in patients with DM (odds ratio [OR]: 1.95, 95%confidence interval [CI] 1.35-2.81; p=0.0004, I2=0%) [16]. Similarly long-term graft patency rates decrease after CABG surgery in patients with DM [17].

Diabetes Mellitus and Heart Failure

Although ischemic heart diseases are an important cause of heart failure, DM is an independent risk factor for the development of heart failure. The reason here is ‘‘diabetic cardiomyopathy’’, which is caused by diabetes by causing damage to cardiac myocytes. The term ‘‘diabetic cardiomyopathy’’ was coined after histopathological examination of the heart structures of four heart failure patients who died without initial CAD [18]. In conclusion, cardiomyopathy in patients with DM was evaluated in relation to hyperinsulinemia, autonomic neuropathy, activation of the renin-angiotensin system and microvascular ischemia.

In these patients, heart failure usually develops due to diastolic dysfunction and systolic functions may be normal. Studies using tissue flow Doppler methods in diabetic patients have found 40-75% of diastolic dysfunction without CAD [19]. In a follow-up study of 150,000 diabetic patients, the study baseline heart failure rate was 22.3%. In the following years, its annual incidence was determined as 12.6%. Dyslipidemia, insulin use, microalbuminuria, and poor glycemic control, especially the age of the patient and diabetes, have been shown as risk factors for the development of heart failure [20]. It has also been found that left ventricular hypertrophy can occur without hypertension in diabetic patients [21].

Techniques such as heart transplantation, heart support devices and artificial heart can be used in the treatment of advanced heart failure. The presence of DM may also affect the results of these treatments. In

a retrospective study involving 341 heart failure patients, the effect of DM on clinical outcomes after left ventricular assist device application was investigated. The patients were followed for an average of 16.1 months, and DM was found to be associated with all-cause mortality (hazard ratio [HR]: 1.73; 95% CI 1.18-2.53; p=0.005). In addition, complications such as device-related thrombosis and pump infection were found to be associated with DM (HR: 2.1; 95% CI 1.35-3.18; p=0.001). At the end of their study, the authors emphasized that despite optimal post-operative blood glucose regulation, all-cause mortality increased after left ventricular assist device operation in DM patients [22].

Diabetes Mellitus and Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the population and increases cardiovascular mortality and morbidity [23]. The Framingham Heart study demonstrated that the presence of DM and poor glycemic control are characterized by new-onset AF [24]. It is known that diabetes increases interstitial fibrosis in atrial structures. As a result of obesity-related DM, lipomatous metaplasia develops in the heart and this process ends with fibrosis [25]. Angiotensin II, transforming growth factor-β (TGF-β) signaling and reactive-oxygen species levels increase due to hyperglycemia in diabetic patients. All these substances have cardiac fibrosis stimulating effects [26]. Another factor causing atrial fibrosis is adipokines (Leptin and adiponectin) secreted from epicardial adipose tissue. Angiotensin II increases leptin secretion from wild-type atrial fibroblasts, and leptin triggers TGF-β signaling. Thus, cardiac fibrosis occurs [27]. In addition, the relationship between AF and adiponectin, which has anti-inflammatory and insulin-sensitizing effects, is not clear. Decreased adiponectin levels are associated with increased obesity [28]. However, interestingly, higher circulating adiponectin levels have been associated with increased rates of AF [29].

In addition to being an important factor that increases the incidence of AF in the normal population, DM also affects AF recurrences after treatment. The effect of DM on AF recurrence was investigated in 531 consecutive patients with AF who underwent cryoablation. At the end of the study, the authors identified the presence of DM as an independent predictor for the developmentof AF recurrence [30]. In addition, the incidence of newly emerging AF after surgical operations is affected by the presence of DM [31-34].

Diabetes Mellitus and Carotid Artery Disease

Carotid artery disease is the most important risk factor for stroke in diabetic patients. In patients with carotid artery stenosis (CAS), distal embolisms from plaque are the most important cause of ischemic stroke. In anatomical studies, it has been shown that diabetes leads to a more unstable and vulnerable structure in the carotid artery plaque structure [35]. The pathogenesis of CAS in diabetic patients is based on insulin resistance, obesity, hyperlipidemia and hypertension.

Carotid intima-media thickness is an important predisposing indicator for CAS and cerebrovascular events. Studies have shown that this thickness is increased in diabetic patients compared to non-diabetic patients. In addition, it has been shown that high blood sugar values in diabetic patients are an important factor for intima-media thickness [36].

In addition to affecting the development of CAS, DM also affects clinical outcomes after CAS treatment, as in other vascular diseases. The results of patients with CAS over 70% who were given the best medical treatment and who underwent carotid endarterectomy with this treatment were compared. During this period, the patients were followed up for an average of 60.7±37.5 months. In this study, the presence of DM increased the risk of stroke in both groups, but it also affected restenosis rates in patients who underwent surgery [37]. A meta-analysis including 18 studies and 17,106 patients also showed that the rates of restenosis after surgical carotid revascularization are increased in patients with DM [38]. In another study involving a large cohort of patients who underwent carotid artery stenting, post-procedure stroke and mortality were also found to be higher in patients with DM [39].

Diabetes Mellitus and Peripheral Artery Disease

The clinical condition that occurs when atherosclerosis especially affects the peripheral vessels of the lower extremities is known as Peripheral Arterial Disease (PAD). Less commonly, upper extremity arteries may also be affected. PAD is an important cause of mortality as well as creating an important morbid con-

dition by causing extremity loss. Although PAD occurring in diabetic patients is similar to the normal population, it mostly affects the distal vascular structures [40]. In the Rochester study, the rate of PAD was found to be 15% in 10 years after the diagnosis of DM, and 45% after 20 years [41].

DM negatively affects the development of PAD as well as post-treatment outcomes. In the study in which the revascularization results of 26,799 PAD patients from the Veterans Affairs data set were investigated, 59.9% of the patients had DM. At the end of the study, it was shown that patients with DM and patients with poor blood glucose control had significantly more poor clinical outcomes [42].

Approximately 100,000 major leg amputations are performed each year in the United States, half of which are due to DM and PAD. In patients with critical leg ischemia, the DM rate is given in the range of 27-76%. The coexistence of DM and PAD can increase amputation rates up to 4 times [43, 44].

Ulcers occurring on the feet due to DM is a clinical condition characterized by motor-sensory loss and impaired wound healing, which poses a risk of amputation. PAD accompanies 50% of this patient group [45]. In addition, a 1-year mortality rate was reported as 40.4% in patients undergoing amputation due to critical limb ischemia [46]. The severity of the situation becomes evident when it is considered that the 5-year mortality is 10% in breast cancer patients, 35% in colon cancer and 50% in myeloma [47].

Diabetic Foot

About one-quarter of patients with DM develop diabetic foot once in their lifetime [48]. This condition occurs with the combination of peripheral neuropathy and arteriopathy due to uncontrolled blood sugar. Depending on the loss of sensitivity due to neuropathy, there may be uncontrolled contacts with external surfaces. As a result of peripheral arteriopathy accompanying this condition, healing is impaired and infection may be added to it [49] (Fig. 2). It also plays a role in Charcot arthropathy, which includes progressive destruction of bones, joints and soft tissues, especially the feet, in diabetic patients [50]. All these situations lead to serious socioeconomic problems.

In these patients, glycemic control should be done well in order to prevent the progression of peripheral neuropathy. Close dialogue should be established in order to achieve target hemoglobin (HbA1c) values in patients [51]. A Cochrane review analysis of 11 randomized controlled trials showed that educating patients on this issue may reduce the risk of diabetic foot [52]. Footwear is also one of the important factors that play a role in the development of diabetic foot. Tight clothing, which is uncomfortable for the feet, may cause foot wounds, as well as a predisposing factor for fungal infections [53].

Diabetes Mellitus and Aortic Aneurysm

Although DM is known to increase cardiovascular diseases, it is negatively associated with the develop-

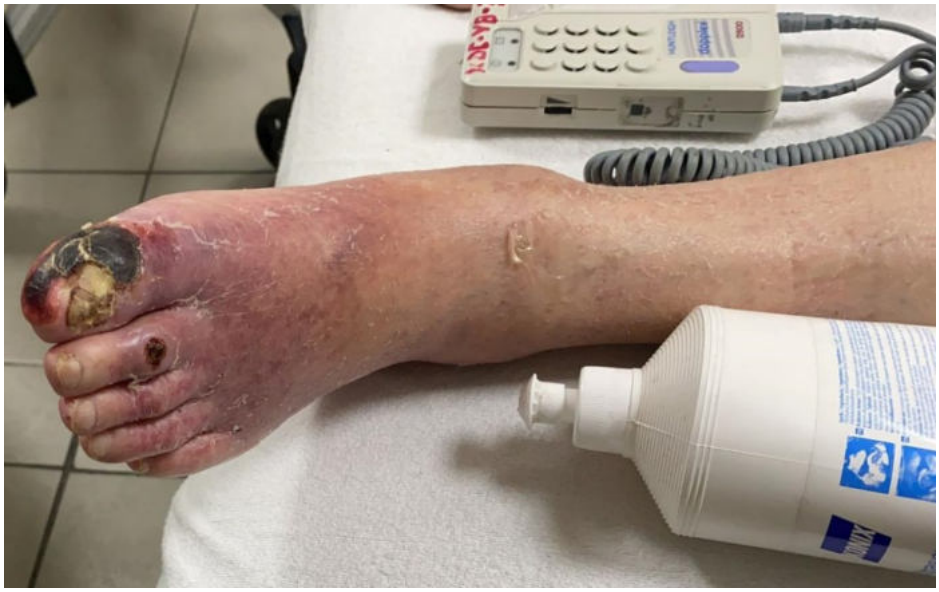

Fig. 2. Imaging of the diabetic foot.

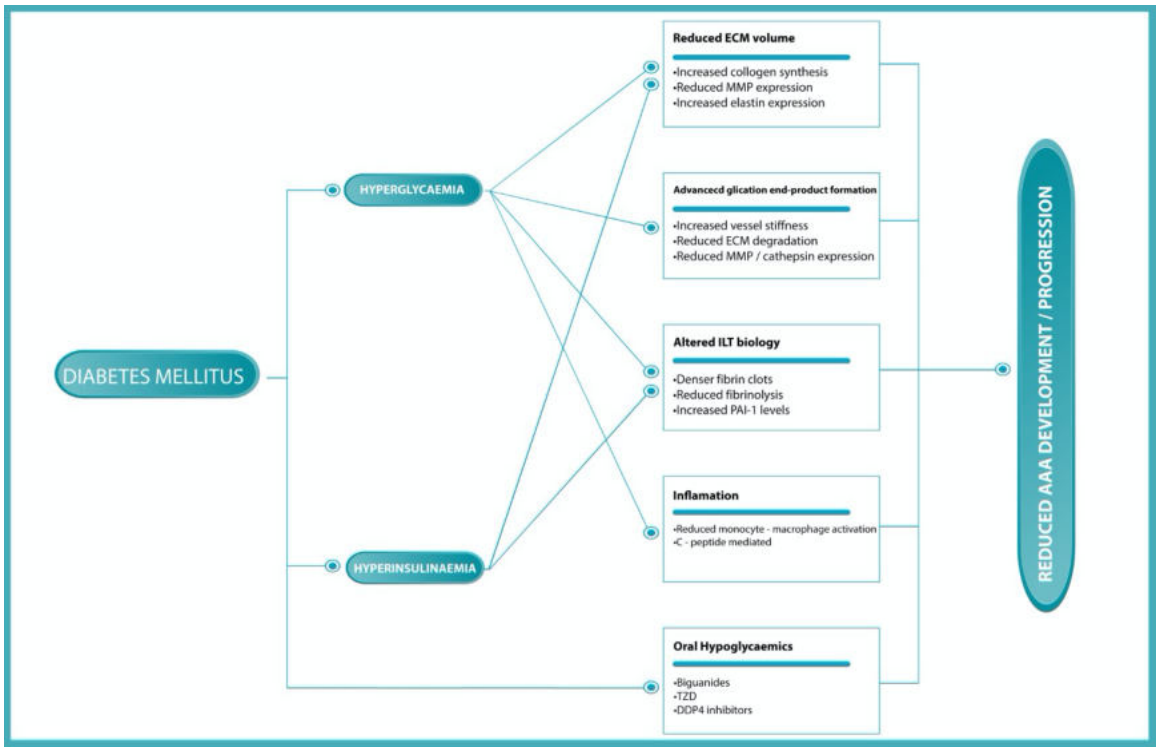

Fig. 3. Potential mechanisms by which diabetes mellitus protects against abdominal aortic aneurysm development and progression. DPP4 = dipeptidyl peptidase-4, ECM = extracellular matrix; ILT = intraluminal thrombus, MMP = matrix metalloproteinase, PAI = plasminogen activator inhibitor, TZD = thiazolidinedione.

ment of abdominal aortic aneurysm (AAA). Although patients with DM have increased arterial calcifications compared to patients without DM, this is not sufficient to explain the reduced aortic dilatation in patients with DM [54, 55]. The explanation of this inverse relationship is basically made in four biological ways. These basic pathways can be listed as follows (Fig. 3) [56]: (1) Extracellular matrix volume, (2) Extracellular matrix glycation and advanced glycation end-product formation, (3) Inflammation and oxidative stress, and (4) Intraluminal thrombus biology.

CONCLUSION

2019 European Society of Cardiology (ESC) Guideline Recommendations for Diabetes Mellitus and Cardiovascular Diseases [57]

(1) DM increases approximately three-fold risk of developing cardiovascular disease. This risk increases with the duration of diabetes and comorbidities (Other previous vascular disease, kidney disease, etc.).

(2) Despite all medical, interventional and surgical treatments for cardiovascular diseases, the prognosis in patients with DM is worse than those without DM. This situation defined as residual risk.

(3) Fasting blood glucose and HbA1c values should be measured in patients presenting with signs of cardiovascular disease and the patient should be examined for DM. If results cannot be obtained with these evaluations, an oral glucose tolerance test should be used.

(4) In patients with DM, management of blood glucose, blood pressure, blood lipids and antiplatelet therapy should be done carefully. This treatment should be planned appropriately for each patient.

(5) Since cardiovascular risk management in patients with DM is complex and difficult, new algorithms should be developed for treatment decisions.

(6) Blood pressure targets should be updated in patients with DM.

(7) LDL-C target should be set below 55 mg/dL in very high risk patient groups, with the use of proproteinconvertase subtilisin/kexin type 9 inhibitors if unachievable with intensive statin therapy plus ezetimibe.

(8) Aspirin therapy should be considered in high and very high risk patient groups. In addition to aspirin

therapy, low-dose novel oral anticoagulant therapy may be considered in patients with coronary syndrome or peripheral artery disease.

(9) The new glucose lowering agents, sodium-glucose co-transporter-2 inhibitors and Glucagon-like peptide-1 receptor agonistsare recommended as first-line therapy in type 2 DM with established cardiovascular disease or high/ very high cardiovascular risk.

(10) Ideas should be generated about DM!

Authors' Contribution

Study Conception: ŞY, AKA, ME; Study Design: ŞY, AKA, ME; Supervision: ŞY, ME, NK, SC; Funding: ŞY, AKA, ME; Materials: ŞY, AKA, ME; Data Collection and/or Processing: ŞY, AKA, ME; Statistical Analysis and/or Data Interpretation: ŞY, ME, NK, SC; Literature Review: ŞY, ME, NK, SC; Manuscript Preparation: ŞY, ME, NK, SC and Critical Review: ŞY, ME, NK, SC.

Conflict of interest

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

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