Review Article

Diabetic peripheral arterial disease in COVID-19 pandemic

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Both diabetes and peripheral arterial disease (PAD) have complex interactions with COVID-19. PAD is one of the most important underlying factors in the development of diabetic foot. The COVID-19 pandemic has also caused an increase in cardiovascular complications in those with chronic diseases, including diabetics, due to both the thrombophilic course of the viral disease and the lockdown measures applied for prevention. Since both COVID-19 and diabetes mellitus predispose to thrombosis, PAD is likely to have a more severe course in diabetic patients with COVID-19. The aim of our study is to discuss the complications, prophylaxis, and treatment of PAD, which is a serious complication of diabetes, during the pandemic period.

Key words: Amputation, COVID-19, diabetes mellitus, peripheral arterial disease

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INTRODUCTION

Peripheral arterial disease (PAD) is an atherosclerotic occlusive vascular disease that usually affects the lower extremities[1] and is an important health problem worldwide, associated with high levels of both mortality and morbidity. Patients with diabetes have a much higher risk of developing PAD, and the course of the disease is more severe and progresses more rapidly than in nondiabetics.[1] COVID-19, a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is likely to predispose a role in the development of thrombotic disease, as it is characterized by excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[2] Both diabetes and PAD have complex interactions with COVID-19. COVID-19 may be associated with an increased risk of leg or digital ischemia.[3] Diabetic patients also show a more severe course of COVID-19.[4]

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In Türkiye, as in other countries, restrictive measures were taken to prevent the exponential spread of COVID-19. Measures such as the lockdown to prevent the transmission of this contagious viral disease have had a devastating impact on diabetic patients with PAD.

During the COVID-19 pandemic, it has been reported that limited access to routine outpatient care and elective surgery can have potentially dramatic consequences.[5] In addition, diabetic patients' reluctance to go to the hospital for fear of exposure to SARS-CoV-2 has led to many problems. Thus, this viral pandemic has adversely affected diabetic patients and triggered the emergence of new diabetes cases.[6]

Diabetes is considered an important risk factor for the development of coronary heart disease and PAD.[7] Moreover, in diabetic patients with PAD, especially in patients without a history of coronary artery disease, guideline-directed medical treatment has been suboptimal.[8]

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PAD and diabetes mellitus increase the risk of each other. Diabetes is considered a risk factor for systemic atherosclerosis. PAD is a reflection of systemic atherosclerosis[9] and occurs earlier in diabetic patients and progresses more rapidly to critical lower-extremity ischemia.[10] Moreover, diabetic patients with COVID-19 are more susceptible to lower-extremity complications.[11] Since both COVID-19 and diabetes mellitus predispose to thrombosis, we could predict that PAD is likely to have a more severe course in diabetic patients with COVID-19. In this study, we aimed to review the effects of SARS-CoV-2, which predisposes to thrombosis, in diabetic patients with PAD. Therefore, we discussed the prophylaxis and treatment of diabetic lower-extremity arterial disease, which can lead to diabetic vascular complications and amputation during the pandemic period.

DIABETIC COMPLICATIONS

Specifically, there are two types of diabetic vascular disease. The first is a nonocclusive microcirculatory disorder involving the renal capillaries and arterioles, retina, and peripheral nerves. The second is a macroangiopathic circulatory disorder characterized by atherosclerotic lesions of the coronary and peripheral arteries.[12] It has been proposed that hyperglycemia is responsible for both micro- and macrovascular complications of diabetes.[13]

Microvascular dysfunction in diabetic patients is characterized by increased vascular permeability and impaired autoregulation of vascular tone and blood flow. These changes result in nephropathy, retinopathy, and neuropathy and possibly contribute to the cardiovascular system complications seen in diabetic patients.[12] Diabetic macrovascular involvement is the result of atherosclerosis and vascular calcification.[14]

IMPORTANCE OF GLYCEMIC CONTROL

In diabetic patients, increased glycemia levels lead to many changes in almost every tissue type. However, the most detrimental effects occur in arterial tissue, increasing the incidence of peripheral and coronary artery diseases.[15] In fact, hyperglycemia itself was associated with immune system impairment, complement fixation, or altered cytokines and chemokine production that enhanced SARS-CoV-2 replication.[16] The benefit of intensive glycemic control on macrovascular complications in diabetics has not yet been demonstrated in randomized clinical trials, but several epidemiological studies reported a correlation between increased cardiovascular disease rate and chronic hyperglycemia.[17,18]

In diabetic patients, hyperglycemia causes endothelial damage, hyperlipidemia, and an increase in platelet viscosity and activity, and atherosclerosis develops over time.[19] Poor blood glucose control accelerates the manifestation of PAD in diabetics.[20] Hemoglobin A1c (HbA1c), an endogenous advanced glycation end product, is a clinically important biomarker that reflects the average glucose concentration in long-term follow-up.[21] If HbA1c is >7%, both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) may be associated with vascular events.[22] In the UK diabetes study, it was reported that every 1% increase in HbA1c was associated with a 28% increase in the incidence of PAD, independent of other risk factors.[23] The American Diabetes Association guidelines recommend that the target HbA1c level should be below 7.0% in patients with diabetes mellitus to prevent microvascular complications.[24]

Vitamin D levels may be related to glycemic control in patients with T2DM.[25] It was reported that low Vitamin D status could be associated with the highest HbA1c level (>8).[25] Magnesium (Mg) deficiency can also worsen glycemic control in patients with T2DM.[26] Mg is also required to activate Vitamin D.[27] The increase in Vitamin D and Mg deficiency as a result of insufficient sunbathing due to quarantine and feeding with industrial agricultural products instead of natural agricultural products is likely to increase health problems even more.

PREVALENCE

The prevalence of diabetes mellitus, which can almost now be called a low-rate pandemic, is increasing rapidly.[28] In Türkiye (a Eurasian country), it is predicted that the rate of patients with diabetes will increase to 20% in the very near future.[28] Epidemiological data revealed a higher mortality rate from COVID-19 among the elderly population with preexisting comorbidities, including diabetes.[4,29] Age- and gender-based analyses from large epidemiological studies show that the risk of PAD in diabetics is almost three times greater than in nondiabetic individuals.[14,30] The Framingham study reported that diabetes mellitus is a strong risk factor for atherosclerotic peripheral arterial and coronary heart disease, independent of other atherogenic risk factors, with twice the average risk for men and three times the average risk for women.[31]

In the general population, patients with PAD have a two to six-fold higher risk of cardiovascular and cerebrovascular events than those without PAD.[32] The prevalence of PAD in elderly patients with T2DM was 31.5%.[33] However, in a study of 200 patients with T2DM aged between 31 and 90 years, the prevalence of PAD was found even higher (38.5%).[34] A study conducted in Egypt also

concluded that peripheral vascular disease is strongly associated with lower-extremity complications associated with diabetes mellitus.[35] Indeed, Boyko *et al*. reported that PAD was associated with a threefold increased risk for lower-extremity amputation.[36] Asymptomatic PAD was found in 17.9% of Turkish diabetic patients in vascular Doppler examination.[37]

IMPORTANCE OF DIABETIC NEUROPATHY

In diabetics, pain perception is likely to be blunted due to peripheral neuropathy. Therefore, diabetic patients with PAD are more likely to present with ischemic ulcers or gangrene than nondiabetic patients.[38] The development of diabetic neuropathy indicates that T2DM has begun to affect capillaries adversely.[39] This suggests that diabetic neuropathy may be closely related to the progression of PAD.[13]

In COVID-19, the beta cells of the pancreas may be damaged due to the pro-inflammatory cytokines triggered by SARS-CoV-2.[40] Vitamin D may have a possible role in the pathogenic mechanisms that predispose to T2DM by modulating insulin resistance and/or pancreatic β-cell function.[41] Zhao *et al*.[42] found that calcitriol stimulated the secretion of nerve growth factor in rat RSC96 cells. This indicates that Vitamin D may be an independent protective factor for neuropathy.[42] However, the protective role of Vitamin D against viral damage in beta cells needs to be supported by further studies.

A recent review and meta-analysis reported that Vitamin D has a significant effect on diabetes mellitus and its associated neuropathy.[43] Normalization of serum Vitamin D level was associated with a reduction in diabetic neuropathy symptoms and signs.[44] Vitamin D supplementation improves neuropathic symptoms by 50% in diabetics with Vitamin D deficiency.[45] Vitamin D deficiency leads to insulin secretion deficiency and glucose resistance.[46] As a result of the improvement in Mg and Vitamin D levels, improvement in neuropathic pain was observed.[47]

DIABETIC FOOT ULCER

Diabetic foot ulcer (DFU) is a serious complication, affecting 15% of diabetic patients throughout their lives, and often leads to lower-extremity amputation unless a prompt, rational, multidisciplinary approach to treatment is followed.[20] Neuropathy was reported in 80% of patients with DFU, and it facilitates ulcer formation by reducing the feeling of pain and pressure sensation.[48]

In the pathophysiology of DFU, besides neuropathy and trauma with secondary infection, the contribution of occlusive PAD is also important.[19] PAD and neuropathy equally contribute to the formation of leg ulcers leading to amputation in diabetic patients.[49] Approximately half of the patients with DFU have PAD, and this association becomes more pronounced with advancing age.[50] Patients with diabetes mellitus and PAD are more likely to have signs of aggressive disease, such as worsening lower-limb function, arterial thrombosis, and ischemic ulceration, compared with patients with PAD alone.[51]

In a meta-analysis including seven studies, Dai *et al*.[52] found that Vitamin D levels were significantly reduced in patients with DFU. It has been reported that Mg supplementation, which has a positive effect in those with DFU, may also reduce the death rate in critically ill patients with T2DM.[53] We think it is important to avoid Mg and Vitamin D deficiencies to reduce the risk of DFU.

Vitamin B12 deficiency is an important risk factor for peripheral neuropathy and DFU.[54] The risk of developing DFU in patients with Vitamin B12 deficiency was three times higher than those with normal Vitamin B12 levels.[55] Vitamin B12 deficiency is prevalent in patients with T2DM (30%).[56] The most important cause of Vitamin B12 deficiency in diabetics is the long-term use of metformin as the first-line pharmacological treatment of T2DM in clinical practice.[57] Bariatric surgery in obese diabetic patients is also another risk factor for Vitamin B12 deficiency.[58]

Malnutrition is common in patients with wound and is associated with increased infection rates and decreased tensile strength of the wound.[59] Wound healing may be adversely affected if adequate folate is not obtained with food.[60] Nutritional deficiencies lead to chronicity by inhibiting the normal processes that allow wounds to progress. Therefore, folate levels should be maintained at normal levels in diabetics.

MANAGEMENT OF DIABETIC FOOT ULCER

DFU is characterized by a full-thickness wound accompanied by skin necrosis.[55] Therefore, all infected tissues should be debrided, and any accompanying abscess, if present, drained.[61] Although there are different debridement methods such as mechanical, enzymatic, or biological debridement, surgical debridement of all infected and dead tissues is the most effective method.[20] The aim of the surgical debridement is to remove all necrotic tissues.[62]

It has been reported that maggot therapy can also be an effective debridement. Tanyüksel *et al*.[63] reported that as a result of maggot treatment applied in 23 patients with DFU, a complete debridement was achieved, the infection was eliminated effectively, and their wounds healed faster than

other wound care methods. Maggot therapy affects wound healing in three ways. First, the larvae provide mechanical debridement by digesting necrotic and infected tissue on the wound surface. Second, the digestive enzymes secreted by them protect the wound from microorganisms by enzymatic debridement. Finally, the movements of the larvae on the wound surface create a mechanical stimulus and increase the migration of inflammatory cells to the wound site and contribute to wound healing.[64]

In cases of DFU where debridement is not sufficient, surgical correction of bone, soft tissue, and vascular components is required.[62] Since bone abnormalities in the diabetic foot frequently cause ulceration, the ulcer may be corrected by metatarsal head resection or osteotomy.[65]

PERIPHERAL ARTERIAL DISEASE

PAD, a multifactorial disease, has genetic and acquired risk factors in its pathogenesis. Hypertension, dyslipidemia, diabetes mellitus, and smoking are among the most important modifiable risk factors for the development of PAD.[66] In a study involving 280 patients with T2DM, it was found that increasing age, high HbA1c level, and smoking increase the likelihood of developing PAD.[67] It was reported that approximately two-thirds of patients who develop peripheral vascular complications in COVID-19 had a background of arterial hypertension, diabetes mellitus, or hyperlipidemia.[11] Furthermore, some viral agents, such as coronaviruses, have been widely associated with the pathogenesis of T1DM.[68]

ROLE OF THROMBOPHILIA

It was reported that the risk of developing thromboembolic and atherosclerotic diseases is increased in diabetic patients carrying the factor V Leiden (FVL) mutation.[69] It was suggested that the FVL mutation is not only associated with venous thrombosis but also with T2DM.[70] Krekora *et al*.[71] demonstrated an association between FVL mutation and T2DM in the Italian population. In addition, heterozygous FVL mutation and chronic poor glycemic control increase the risk of thrombosis in patients with T1DM.[69]

An inter-society consensus stated that increased homocysteinemia levels could be a stronger risk factor for PAD compared with coronary heart disease.[72] It has been reported that there is a significant relationship between Vitamin B12 deficiency and high fasting homocysteinemia levels and the risk of PAD.[66] Therefore, we could predict that B12 and folate deficiency are likely to lead to a severe clinical course in COVID-19 patients with diabetic peripheral vascular disease, especially those with methylenetetrahydrofolic acid reductase (MTHFR) C677T polymorphism.[73]

As might be predicted, activation of coagulation and associated thromboembolic events are common in patients with COVID-19, and therefore, inherited thrombophilic risk factors may direct the course of the disease in the direction of thrombosis tendency.[72] Indeed, Avci *et al*. (2023) reported that the frequency of FVL mutation in severe COVID-19 patients was higher than in the healthy population.[74] Since both COVID-19 and diabetes predispose to thrombosis, we could predict that this contagious viral disease will be more severe in diabetic patients with PAD.

ANATOMIC LOCALIZATION OF PERIPHERAL ARTERIAL DISEASE

Diabetes also enhances the outcomes of PAD as it involves more distant acral vessels and can cause medial sclerosis and accelerate vascular stiffening through mechanisms such as oxidative stress, genetic damage, and vascular injury.[75] In diabetics, infragenicular leg arteries are involved rather than the femoropopliteal artery segment. The aortoiliac segment is usually spared.[8]

DIAGNOSIS OF PERIPHERAL ARTERIAL DISEASE

Approximately 50% of patients with critical lower-extremity ischemia and 30% of patients with intermittent claudication have diabetes.[76] Symptoms of PAD, such as pain at rest and intermittent claudication, may not be obvious in diabetic patients because of the accompanying sensory neuropathy.[10] Thus, intermittent claudication, the best-known symptom of PAD, occurs in only 25% of patients with diabetes and PAD.[10]

Peripheral artery involvement in COVID-19 patients may be manifested as acute limb pain, paresthesia, livedo reticularis, gangrene, or asymptomatic chilblain-like lesions.[11] For the diagnosis, a comprehensive history should be taken and a systemic physical examination should be performed. Skin changes should be carefully examined on the lower extremities [Figure 1]. Pulses of the lower-extremity arteries should be palpated bilaterally. In 30% of healthy individuals, the dorsalis pedis pulse may not be palpable.[77] Therefore, the absence of both the dorsalis pedis pulse and the posterior tibial pulse should strongly suggest the presence of PAD.[1] Venous Doppler ultrasonography should also be performed in diabetic patients requiring peripheral bypass surgery [Figure 2].

PROPHYLAXIS

Diabetic patients with PAD face a significantly increased risk of major complications, including amputation, compared with patients with diabetes only or PAD only.[78] Complications are likely to increase further in these patients

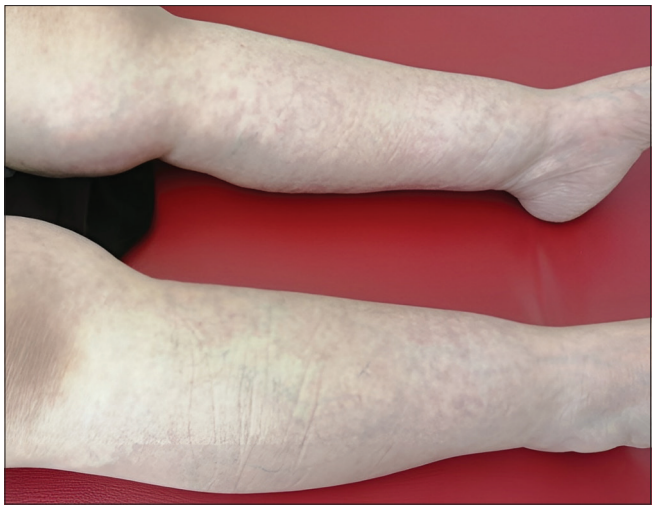

Figure 1: Livedo reticularis on the lower limbs in a diabetic patient

if infected with COVID-19. Since the main predisposing factors for the development of DFU are neuropathy and PAD, it is important to protect the neurosensory and vascular systems of the lower extremities.[48] PAD in diabetics shows a faster course. Moreover, COVID-19 can cause acute arterial and venous complications that must be recognized and treated promptly.[79] Thus, adequate use of HbA1c testing, diabetic foot care, and vascular evaluations should never be compromised in these patients.[53]

TREATMENT

Foot examination should be performed carefully. The course of neuropathy should be slowed down by maintaining the glycemic level within normal limits and a healthy lifestyle. Exercise is considered the most effective noninvasive treatment to improve pain symptoms and ambulation in patients with intermittent claudication.[4] The deprivation by walking exercises of diabetics with peripheral vascular disease has been a serious problem. As is known, walking exercise is the first-line treatment for peripheral vascular disease.[5] However, if the patient is in the risk group for DFU, exercise should be evaluated carefully.[48] Exercise is prohibited in some conditions, such as uncontrolled hypertension, autonomic neuropathy, and peripheral neuropathy.

A supervised exercise program with cilostazol therapy is the preferred initial therapy for the management of PAD disease. However, cilostazol should not be used in patients with heart failure (systolic or diastolic) because of concerns about the potential risk of mortality.[51] Revascularization should be considered if lifestyle changes and pharmacological treatment prove inadequate.[1]

When the ulcer does not heal within 4–6 weeks despite appropriate treatment, vascular imaging should be

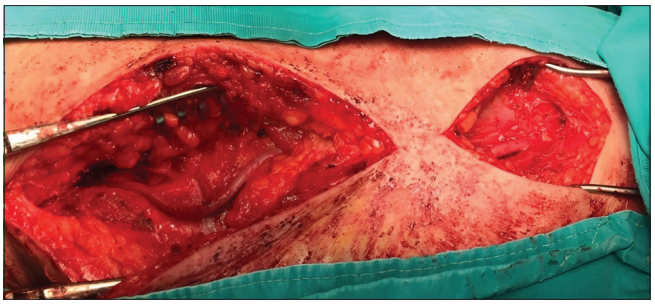

Figure 2: Intraoperative photograph showing the saphenous vein bypass graft in a diabetic patient with severe peripheral artery disease

considered. Based on vascular imaging findings, the most appropriate revascularization procedure should be performed if necessary.[48,80,81] The aim of revascularization is to improve wound or ulcer healing, to treat insufficiently intermittent claudication or resting pain, to prevent possible amputation, or to improve postamputation wound healing.[62]

While the use of endovascular procedures for peripheral vascular disease is markedly increasing, open bypass surgery is critical for successful limb salvage in patients with diabetic foot.[82,83] Open surgical revascularization in diabetes tends to have greater durability compared to endovascular procedures. Autogenous saphenous vein bypass to the patent distal lower-extremity arteries is the most preferable method of restoring blood flow to the threatened extremity.[51]

Collateral vessel formation is impaired in diabetics, which is among the reasons why tissue ischemia is more severe compared to patients without diabetes.[84] Since peripheral collateral circulation contributes significantly to lower-extremity nutrition in diabetic patients with severe PAD,[21] care should be taken to preserve collateral circulation during surgery. After a successful vascularization process, positive results are often obtained with multidisciplinary teamwork. Undoubtedly, the patient should be in harmony with the team. The fight against hyperglycemia, hypertension, and hyperlipidemia should be continued and smoking should be avoided.[62]

AMPUTATION

Diabetes, leading to DFU, has remained the primary cause of nontraumatic lower-extremity losses globally.[48] In diabetic patients, neuropathy, peripheral vascular disease, and infection contribute to lower-limb amputation.[35] Approximately 50% of diabetic patients with DFU have severe infections and 10%–15% have moderate infections.[85] To save the affected extremity, it is necessary to control the infection in the wound. The risk of extremity loss is high in cases with septic disease presenting urgently with large and infected wounds.[14]

Patients with diabetes have a 15-fold increased risk of amputation.[1] Amputation is one of the most devastating complications that might be experienced in diabetic patients with PAD. The complications of diabetes, including amputation, are more frightening than the disease itself.[86] Wukich *et al*.[87] reported that diabetics feared major lower-limb amputation compared with death, end-stage renal disease, and blindness. When diabetes is accompanied by PAD, the risk of infection, amputation, and cardiovascular and cerebrovascular events increases, and the healing of foot ulcers is adversely affected.[51,88,89] Because of endothelial dysfunction secondary to diabetes or hypertension, peripheral gangrene is more likely in diabetic patients infected with SARS-CoV-2.[11,90]

CONCLUSION

As it is known, COVID-19 creates a tendency to thrombosis. If we accept COVID-19 as a thrombophilic risk factor, close follow-up of diabetic patients with PAD recovering from COVID-19 with intermittent vascular Doppler studies should not be neglected. In addition, we should never neglect face-to-face systemic physical examination, especially in diabetic patients, during and after the pandemic.[91] Although the pandemic seems to be losing its effect, it is likely that the negative effects will continue for a while. Indeed, the long-COVID-19 phenomenon has already drawn attention. In conclusion, the pandemic has exacerbated the problems in diabetic PAD. However, these problems are likely to be overcome with the necessary prophylactic and therapeutic approaches.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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