Journal of Diabetes Research

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Research Article

Amputations of Lower Limb in Subjects with Diabetes Mellitus: Reasons and 30-Day Mortality

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Background. Diabetic foot is one of the leading causes of patient disability worldwide. Lower-extremity amputations (LEAs) resulting from this disease massively decrease quality of life, the function of the patient, and incur significant healthcare costs. The aim of this study was to assess trends in the number of amputations, the diagnosis at discharge, and diagnosis-related mortality after LEA procedures in a nationwide population. *Methods*. Datasets of the National Heath Fund containing information about all services within the public healthcare system in Poland, spanning the years 2010-2019, were analyzed. The source of data regarding mortality was the database of the Polish Ministry of Digital Affairs. *Results*. Between 2010 and 2019, the annual number of amputations in patients with diabetes increased significantly from 5,049 to 7,759 (p for trend < 0.000001). However, the number of amputations in patients with diabetes calculated as a number per 100,000 diabetics decreased significantly (p for trend < 0.0005) during this period. Amputations in patients with diabetes accounted for a majority of all amputations; the mean percentage of amputations in patients with diabetes was 68.6% of all amputations (from 61.1% in 2010 to 71.4% in 2019, p for trend < 0.0000001). The most common disease diagnosed at discharge after LEA in diabetic patients was diabetes itself. Vascular pathologies, such as soft-tissue/bone/joint infections and ulcerations, were the next most common. The 30-day mortality rate after LEA was rather high in patients with, as well as without, diabetes (depending on the cause for amputation 3.5-34% and 2.2-28.99%, respectively). *Conclusions*. The number of LEA in patients with diabetes in Poland increased substantially between 2010 and 2019 along with an increasing number of diabetics. Vascular pathologies, infections, and ulcerations were the most common causes of LEA. The 30-day mortality rate after amputation was rather high and varied depending on the diagnoses at discharge.

1. Introduction

Diabetes mellitus is one of the fastest growing public health concerns. The prevalence of diabetes has increased in recent decades, in most developed and developing countries. Data from the Global Burden of Disease Study 2017, assessing the global, regional, and national burden and trend of diabetes in 195 countries and territories, indicate that the 2017 global prevalence of diabetes was 476.0 million. This number is expected to increase to 570.9 million in 2025 [1]. The number of patients with diabetes is also increasing in Poland—in 2014, there were 2.113 million cases, followed by 2.533 million cases in 2017 [2].

Chronic hyperglycaemia, associated with poorly controlled diabetes, causes damage to various organs and systems and induces chronic diabetes complications, leading to incapacity, reduced quality of life, and ultimately death. One of the most common complications of diabetes is a diabetic foot. Pathologies that are risk factors for the occurrence of a diabetic foot occur quite common in diabetic patients,

e.g., in a study conducted in Wroclaw (Poland), it was found that 7.28% of diabetic patients have peripheral neuropathy; 35.37%, calluses; 24.2%, foot deformities; and 17.39%, features of the pathology of arterial vessels [3].

Diabetic foot syndrome may result in lower-extremity amputation. According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), in 2016, about 131 million people (1.8% of the global population) had diabetes-related lower-extremity complications, including 6.8 million amputations [4]. It should be noted that cases with diabetes account for 60-70% of all lower-extremity amputations (LEA) [5, 6]. Diabetes-related lower-extremity complications are a large and growing contributor to the disability burden worldwide [4]. Lower limb amputation concurrently leads to an increase in illness-related costs and a huge change in the quality of life and function of the patient. After LEA, patients have a diminished quality of life compared to the general population [7]. A review of studies from India indicates that the prevalence of psychiatric disorders among this group of patients can be in the range of 32% to 84%, including depression rates of 10.4%–63% and posttraumatic stress disorder of 3.3%–56.3% [8]. Another problem to consider in this population is the incidence of phantom limb pain and residual stump pain.

Lower-extremity amputations are also related to significant early and long-term postoperative mortality. In a national study performed in New Zealand on individuals diagnosed with diabetes, more than 11% of patients who underwent major amputation died within 30 days, whereas nearly 18% died within 90 days [9]. In another population-based cohort study conducted in Italy, including patients with diabetes undergoing a primary amputation, mortality rates at 1 and 4 years were 33% and 65%, respectively, for major LEA and 18% and 45% for minor LEA [10].

The aim of this study was to assess trends in the number of amputations, the reasons for them, and the diagnosis-related mortality after LEA procedures in patients with diabetes compared to the nondiabetic population.

2. Methods

2.1. Data Sources. The source of health-related data is the Polish National Health Fund. The analyzed datasets contain information about all services within the public healthcare system in Poland, spanning the years 2010-2019. The data contains an anonymized patient identifier, which allows the analyses to be made at the individual level. Each service within the public healthcare system (for example, hospitalizations, which were assessed in this paper) has an assigned ICD-10 code, which is put into the system by the healthcare professional who treated the patient. Additionally, in the case of surgical hospitalizations, information about surgical procedures performed within the service (like hospitalization) is also introduced into the system. The source of data regarding mortality is from the database of the Polish Ministry of Digital Affairs. The information is based on death certificates given out by registry offices; however, only the date of death, but not the cause, is accessible in this database. Both databases contain the same patient identifier, and therefore, the information can be merged. The source of Poland's population data is Statistics Poland.

2.2. Definition of the Diabetic Population. A person was considered diabetic when he/she had at least one diabetic ICD-10 code (any code within the E10-E14 range) reported as the main reason for the service within the public healthcare system. The registered diagnosis date was identified as the date of the very first issuance of a relevant diabetic ICD code. The diabetic population in a given year was defined as the registered prevalence at the end of the year (December 31st). Specifically, the population was composed of diabetic patients who had been diagnosed up until the end of that year and had not yet died.

2.3. Amputations and Diagnoses at Discharge. The procedures analyzed in this paper are amputations of the lower limb (either of feet, toes, parts of feet, or other below-knee amputations). All of the ICD-9 procedures used in the database search are listed in Table 1. The diagnoses at discharge after the LEA procedure were categorized by ICD-10 codes, which during the examined years (2010-2019) were reported as the main diagnosis for the hospitalization during which the amputation procedure was performed. The specified categories were diabetes, vascular (atherosclerosis and gangrene), sepsis, acute conditions, infections of soft tissues (skin, subcutaneous tissue, or muscles), ulcerations, infections of bones or joints, trauma (including burns and frostbites), neoplasms, or others. All ICD codes that were included into a specific category are given in Table 1.

Diabetic amputations were defined as amputations which were performed on diabetic patients, no earlier than 30 days before the diabetes diagnosis. In other words, amputations predating the diabetic diagnosis by up to 30 days were considered diabetic. This is because of the relatively common situation where the diabetic foot diagnosis is the first manifestation of a patient's diabetes. On the contrary, nondiabetic amputations were defined as amputations in patients never diagnosed with diabetes. In effect, these parameters excluded patients, in whom diabetes was diagnosed more than 30 days after the amputation, from the analysis. The number of patients excluded by these parameters totalled 2,710 during the 10 years of being analyzed.

2.4. Statistical Analysis. The absolute number of all amputations and the number of amputations per 100 thousand inhabitants was determined. In the population with diabetes, the number of amputations per 100 thousand diabetic patients was also determined. The percentage of diabetes and nondiabetes amputations was calculated. The statistical significance for trends was assessed using an extended Mantel-Haenszel chi-square test for linear trend [11].

3. Results

3.1. Number of Amputations. The number of amputations in patients with diabetes increased substantially between the years 2010 and 2019 (from 5,049 to 7,759, p for trend $<$ 0.000001). In comparison, the number of amputations in patients without diabetes was stable (3,214 in 2010 and

Table 1: ICD-10 codes used for defining the diagnosis at discharge categories and ICD-9 codes used for defining amputation procedure.

Category	ICD-10 codes
Vascular	I70; R02
Bone/joint infection	M00; M01; M02; M03; M04; M05; M06; M07; M08; M09; M10; M11; M12; M13; M14; M15; M16; M17; M18; M19; M20; M21; M22; M23; M24; M25; M86; M87; M90
Soft tissue infection	A18.4; A20.1; A22.0; A26.0; A28.1; A30; A31.1; A32.0; A36.3; A43.1; A44.1; A46; A48.0; A51.3; L00; L01; L02; L03; L04; L05; L06; L07; L08; M60
Ulceration	L88; L89; L97; I83.0; I83.2
Trauma (including burns and frostbites)	S70; S71; S72; S73; S74; S75; S76; S77; S78; S79; S80; S81; S82; S83; S84; S85; S86; S87; S88; S89; S90; S91; S92; S93; S94; S95; S96; S97; 98; S99; T12; T13; T24; T25; T31; T33.6; T33.7; T33.8; T34.6; T34.7; T34.8; T35.5
Neoplasms	C00; C01; C02; C03; C04; C05; C06; C07; C08; C09; C10; C11; C12; C13; C14; C15; C16; C17; C18; C19; C20; C21; C22; C23; C24; C25; C26; C27; C28; C29; C30; C31; C32; C33; C34; C35; C36; C37; C38; C39; C40; C41; C42; C43; C44; C45; C46; C47; C48; C49; C50; C51; C52; C53; C54; C55; C56; C57; C58; C59; C60; C61; C62; C63; C64; C65; C66; C67; C68; C69; C70; C71; C72; C73; C74; C75; C76; C77; C78; C79; C80; C81; C82; C83; C84; C85; C86; C87; C88; C89; C90; C91; C92; C93; C94; C95; C96; C97; D00; D01; D02; D03; D04; D05; D06; D07; D08; D09; D10; D11; D12; D13; D14; D15; D16; D17; D18; D19; D20; D21; D22; D23; D24; D25; D26; D27; D28; D29; D30; D31; D32; D33; D34; D35; D36; D37; D38; D39; D40; D41; D42; D43; D44; D45; D46; D47; D48
Acute	I21; I22; I46; I74; J20; J21: J22; J46: J80; J95: J96; J98; N17; A48.3; R57; T81.1; T79.4; O08.3; O75.1; T78.0; T78.2; T80.5; T88.2; T88.6
Sepsis	A02.1; A20.7; A22.7; A24.1; A26.7; A32.7; A42.7; R09.0; R09.2; R57.8; A54.8; B00.7; B37.7; O75.3; T80.2; T81.4; T88.0; A40; A41; O85; B49
Others	
Diabetes	E10; E11; E12; E13; E14
Amputation	84.1; 84.10; 84.10; 84.101; 84.102; 84.103; 84.11; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31; 84.1; 84.10; 84.10; 84.102; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31; 84.1; 84.10; 84.102; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31; 84.1; 84.10; 84.101; 84.102; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31; 84.1; 84.10; 84.10; 84.102; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31; 84.1; 84.101; 84.102; 84.103; 84.11; 84.111; 84.113'; 4.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 4.31; 84.1; 84.101; 84.10; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31; 84.1; 84.10; 84.10; 84.102; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.151; 84.31; 84.1; 84.10; 84.101; 84.102; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31; 84.1; 84.10; 84.101; 84.102; 84.103; 84.11; 84.111; 84.113; 84.114; 84.119; 84.12; 84.121; 84.122; 84.123; 84.124; 84.125; 84.129; 84.14; 84.15; 84.151; 84.31

3,109 in 2010, not significant). The trends for the number of amputations in diabetic and nondiabetic populations are shown in Figure 1(a). However, the number of amputations in patients with diabetes calculated as a number per 100,000 diabetics decreased significantly during the 10-year period (259.73 in 2010 and 229.99 in 2019, p for trend < 0.0005) while the number of amputations in patients without diabetes calculated per 100,000 inhabitants was stable (8.34 in 2010 and 8.1 in 2019, not significant). Those trends are illustrated in Figure 1(b).

The mean percentage of amputations in patients with diabetes accounts for 68.6% of all amputations. This number slowly increased year over year, beginning at 61.1% in the year 2010 and reaching 71.4% in the year 2019 (p for trend < 0.0000001).

3.2. Diagnoses at Discharge. In patients with diabetes, the most common diagnosis upon discharge from the hospital was "diabetes" (see Table 1 and Figure 2(a)). This diagnosis does not give a precise reason for an amputation, and therefore, the proportion of the remaining diagnoses is altered. A decision was made to show the percentage of the diagnoses used in patients with diabetes which excluded the patients mentioned above (Figure 2(b)).

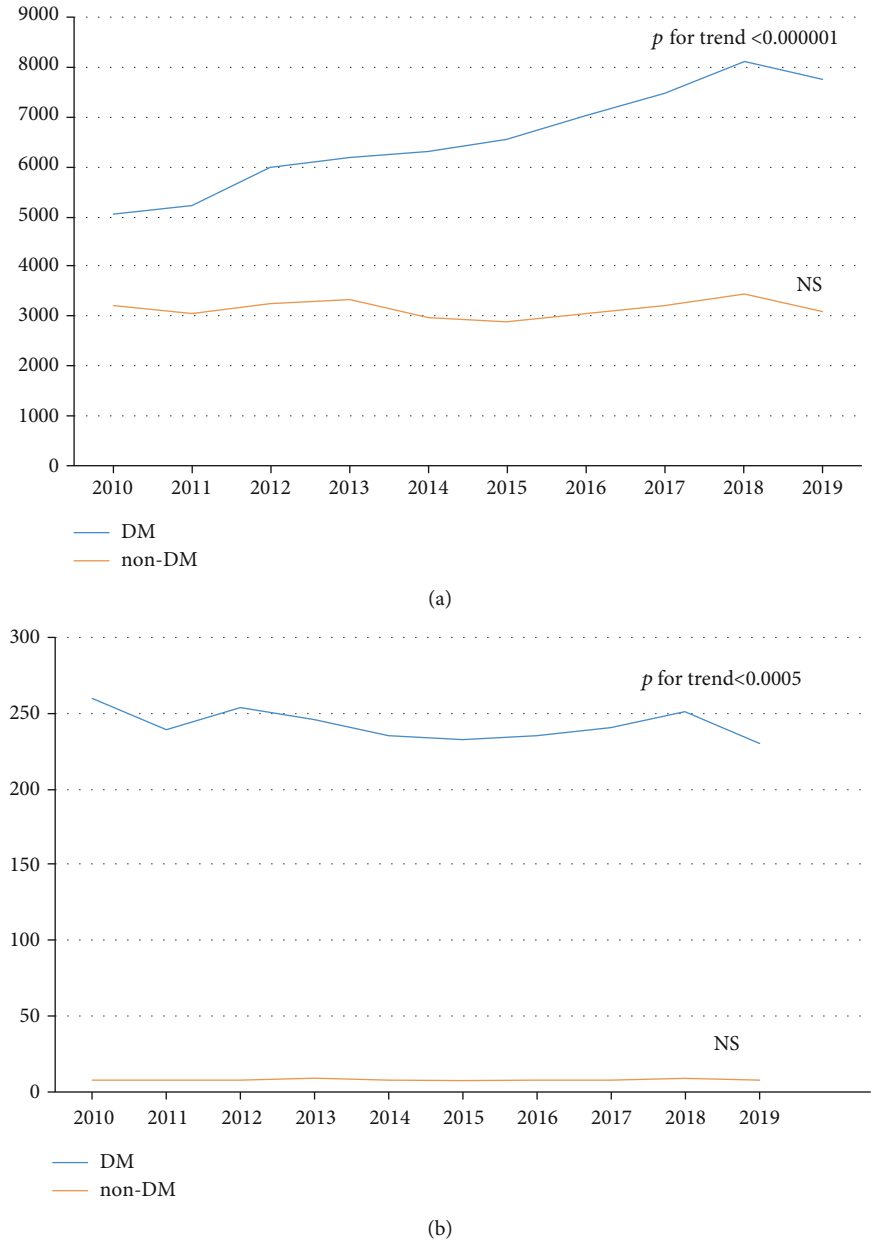

Figure 1: (a) Absolute number of amputations in patients with and without diabetes, and (b) number of amputations in patients with diabetes per 100,000 diabetics, and in patients without diabetes per 100,000 inhabitants in the years 2010-2019.

Furthermore, the proportion of patients in whom an amputation was performed for vascular reasons was similar in diabetics and nondiabetics. The same was true for both bone and joint infections. However, amputations in patients with diabetes were performed more frequently because of soft-tissue infections and ulcerations. On the other hand, trauma and other causes for amputation were more common in patients without diabetes. Sepsis was a rare cause for amputation in both groups, while neoplasms and various acute conditions (see Table 1) were in our opinion, rather concomitant diseases or complications of the procedure, than a reason for amputation (Figures 2(a) and 2(b)).

3.3. Thirty-Day Mortality. The 30-day mortality was rather high. The range varied depending on the reason for amputation, from 3.46 to 34% in patients with diabetes, to 2.24 to 28.99% in patients without diabetes (Table 2). In both groups, mortality was highest in patients with sepsis or acute conditions. In other cases, the 30-day mortality did not exceed 10%.

4. Discussion

In this paper, we have analyzed trends in lower limb amputations in patients with and without diabetes between the years 2010 and 2019 using a large national database. We found that

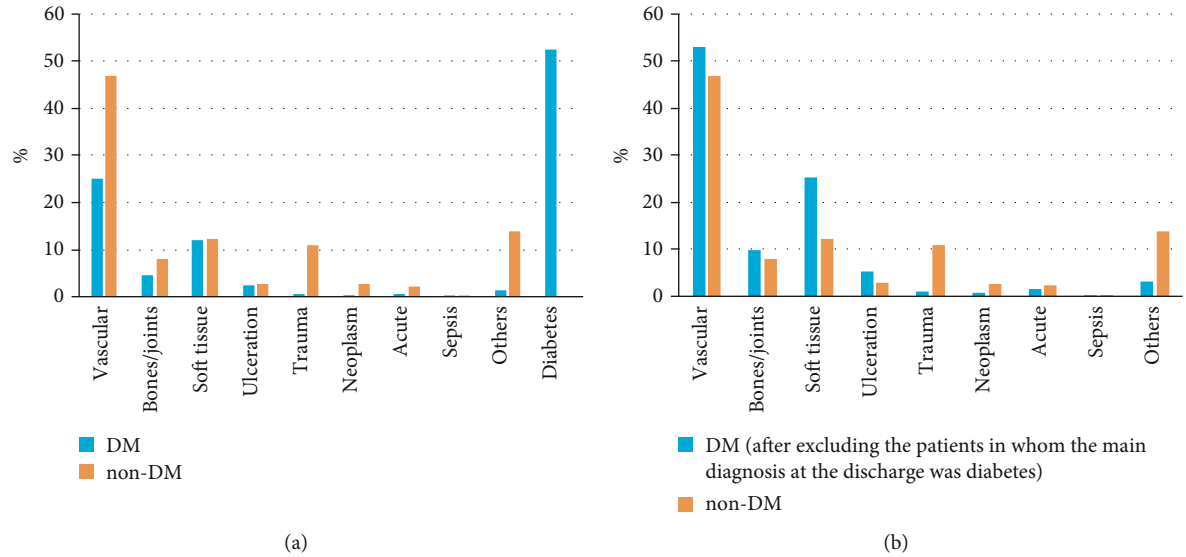

Figure 2: (a) Percentage number of ICD-10 categories given as the main diagnosis at the discharge from the hospital after the amputation in all study population and (b) in population after excluding the patients in whom the main diagnosis at the discharge was diabetes.

Table 2: Thirty-day mortality according to diagnosis at discharge categories in patients with and without diabetes.

Category	Patients with diabetes		Patients without diabetes	
	Number of amputations	Number of deaths (%)	Number of amputations	Number of deaths (%)
Vascular	16515	1383 (8.37)	14785	1421 (9.61)
Bone/joint infection	3030	105 (3.46)	2533	66 (2.6)
Soft tissue infection	7918	47 (5.27)	3871	275 (7.1)
Ulceration	1670	111 (6.64)	868	79 (9.1)
Trauma (including burns and frostbites)	334	20 (5.99)	3470	91 (2.62)
Neoplasms	262	11 (4.2)	847	19 (2.24)
Acute	450	99 (22.0)	700	147 (21.0)
Sepsis	100	34 (34.0)	69	20 (28.99)
Others	948	104 (10.97)	4393	149 (3.39)
Diabetes	34433	1635 (4.74)	—	—

the crude number of amputations in patients with diabetes increased substantially (over 50%) and significantly, whereas the number of amputations in patients without diabetes was stable. We have noted also that if the number of amputations in patients with diabetes was shown as a number per 100,000 diabetics, the amputation rate did not increase but rather decreased significantly during the 10 years of being analyzed. Thus, the reason for the increase in the absolute number of diabetic amputations was the increasing number of patients with diabetes.

The rise in the total number of diabetic amputations was observed also in Spain in 2002-2012 [12], but this large national Spanish study does not present the data in relation to the number of diabetic patients (in this country, the diabetes incidence also rises [12, 13]). In the nationwide study performed in Belgium between 2009 and 2013, just like in our study, the number of LEA significantly declined in individuals with diabetes and remained stable in the population without diabetes [14]. In turn, in the Irish study, performed in 2005-2009, both total diabetes-related and total nondiabetes-related amputation rates did not change significantly [15]. Similarly, in Austria, major lower-extremity amputation rates in diabetic patients remained stable between 2014 and 2017 [16].

It should be emphasized, that generally, the incidence of lower extremity amputation for all reasons in European countries is variable [17]. Even in Poland, the geographic variability of the numbers of major nontraumatic lower limb amputations in diabetics was observed [18]. The number of amputations in every country depends on many factors, i.e., total funding for healthcare, availability of specialists' clinics and highly specialist treatment [18], dedicated wound services and foot care services delivery [19], educational level, and income of patient [20].

In our study, "diabetes" was the most common diagnosis used upon discharge of diabetic patients undergoing LEA from the hospital. As mentioned above, it is obvious that this diagnosis does not identify the precise reason for amputation

but rather is a diagnosis at discharge, and therefore, the proportion of the remaining reasons for diagnoses is altered. Therefore, we have decided to show, additionally and separately, the percentage of the diagnoses used in patients with diabetes excluding the patients mentioned above (Figure 2).

Unfortunately, as in more than 50% of patients with diabetes, the diagnosis at discharge was only "diabetes"; we were not able to determine the real reasons for amputation in those subjects. We also cannot be sure that a diagnosis at discharge was a reason for amputation. Those issues may be regarded as limitations of this study.

It seems however that the main cause of LEA in diabetics is vascular pathology, mainly defined as a discharge diagnosis of atherosclerosis. The proportion of patients in whom amputation was performed for vascular reasons was similar in diabetics and nondiabetics, when the discharge diagnosis of diabetes was excluded. The same was true for bone or joint infections. However, it seems that amputations in patients with diabetes were performed more frequently due to soft-tissue infections and ulcerations. This is of course not surprising, as a history of foot ulcers, osteomyelitis, or gangrene is a well-known risk factor for amputation in diabetes [21]. In the study performed in South Africa, infection and ulcers were the leading causes of LEA in diabetic patients, while ischemia was the most dominant cause in nondiabetic patients [22]. In India, infection was also found to be the leading cause of amputation [23]. However, it should be emphasized that peripheral arterial disease is reported in up to 95% of people with diabetes receiving lower limb amputations [24]. It was shown that amputation risk increases with increasing comorbidity burden, with peripheral vascular disease being one of the major independent risk factors [25]. This seems to be consistent with our study, as atherosclerosis and gangrene are more frequent causes of amputations in diabetes patients, whether the discharge diagnosis "diabetes" was excluded or not.

The 30-day mortality in our study was rather high. The range varied depending on the reason for amputation, from 3.46 to 34% in patients with diabetes, to 2.24 to 28.99% in patients without diabetes. In both groups, mortality was highest in patients with sepsis or acute conditions. We do not have the data regarding the time sequence of the amputation procedure and the diagnosis of sepsis or an acute condition. However, it seems as though those may be a consequence of, rather than a reason for, the procedure, seeing as generally such conditions are at least relative contraindications for surgery. Although there were some differences in mortality rates between diabetic and nondiabetic patients, we do not regard them as clinically significant, as in some diagnoses at discharge categories, mortality is bigger in patients with and in other ones in patients without diabetes and the percentage differences are rather modest. There does not seem to be any regularity with regard to these results.

Multiple comorbidities in diabetic patients are reasons for the increased risk of adverse events, including mortality, in this population. Therefore, it is not surprising that patients with diabetes who underwent surgery have higher risks of complications and mortality compared with patients without diabetes [26–28]. The overall 30-day mortality after major LEA reported in other studies from various countries ranged from 1% to 13.5% [9, 16, 29] and was significantly correlated with age and age-adjusted comorbidity [16]. It has also been shown that after LEA, patients with diabetes had an increased risk of death compared to nondiabetic patients [30]. However, in Ireland, a study performed in a single tertiary referral centre for vascular surgery showed no statistically significant association between mortality rate and comorbid diabetic mellitus in patients who underwent major lower limb amputation [31].

Our study has several limitations. The first one is its retrospective character. Because of this, it is difficult to assess the real reason for each amputation, especially in the patients diagnosed with "diabetes" at discharge, as well as in those for whom the diagnosis at discharge seems to reflect a complication of, rather than the reason for, the procedure (e.g., different acute conditions or sepsis). Other limitations include a lack of data about important risk factors for mortality, like diabetes control, concomitant diseases. However, the errors inherent to a retrospective study may be balanced out by the large size of the population.

5. Conclusions

The number of lower-extremity amputations in diabetic patients in Poland increased substantially between the years 2010 and 2019, whereas the number of amputations in patients without diabetes was stable. This increase is due to the increasing number of patients with diabetes, seeing as the number of amputations/number of patients with diabetes ratio remains stable. The 30-day mortality rate after amputation was rather high and varied with different diagnoses at the discharge after procedures.

Data Availability

All data from the database can be obtained upon reasonable request from Marta Raczynska (m.raczynska@mz.gov.pl).

Conflicts of Interest

Edward Franek is a coauthor of one publication with the guest editor of this issue of JDR. Other authors do not disclose any conflicts of interest with regard to this study.

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Review Article

Patients with Diabetes Complicated by Peripheral Artery Disease: the Current State of Knowledge on Physiotherapy Interventions

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Diabetes mellitus (DM) is one of the major public health problems that account for morbidity, mortality, and disability worldwide. The presence of DM increases the risk of peripheral artery disease (PAD), as well as accelerates its course, making these patients more susceptible to ischemic events and impaired functional status. Unfortunately, alternative treatments for vascular complications in diabetes are poorly researched. Physiotherapy (kinesitherapy combined with different physical therapy agents) in individuals with DM and coexisting PAD may offer an important complementary therapy alternative. Early therapeutic measures can significantly improve patient outcomes, reduce cardiovascular risk, and improve daily life quality. The article provides an update on the current state of knowledge on physiotherapy interventions in the course of DM in patients with coexisting PAD.

1. Introduction

Atherosclerosis is responsible for chronic ischemia of the extremities, mainly the lower ones, in 20–30% of the population over 50 years of age [1]. Peripheral artery disease (PAD) affects approximately 202 million people [2], and progressive atherosclerotic lesions, leading to stenosis and occlusion in the arteries, are the cause of the claudication, which reduces patients' quality of life, and ultimately may be the cause of amputation [1, 3].

Lower extremity atherosclerosis is also one of the major chronic complications of diabetes mellitus (DM), a condition that has become an epidemic of the 20th and 21st centuries. Based on the World Health Organization (WHO) report [4], it is a known fact that the number of people with diabetes is steadily increasing worldwide, and experts estimate that by 2045 there will be at least 629 million people living with the disease [4]. It also means an increase in the number of people affected by its chronic complications. DM is the second (after nicotinism) most significant risk factor for PAD, and patients with diabetes have as much as 2–4 times greater risk of developing atherosclerosis [5, 6]. This risk is influenced by glycemic control—every glycated hemoglobin (HbA1c) increase by 1% is associated with a 28% increase in the relative risk for manifest PAD [6]. In addition, the higher risk of atherosclerosis in patients with type 2 diabetes mellitus (T2DM) is due to numerous metabolic disorders coexisting with hyperglycemia, e.g., unfavorable lipoprotein profile or hypertension. Therefore, all these cardiovascular risk factors should be intently monitored and corrected to prevent the development of major adverse ischemic limb events [7, 8].

Furthermore, both the prevalence of atherosclerosis and T2DM increase with age, which is of epidemiological significance in aging populations. The cooccurrence of lower limb atherosclerosis and diabetes is particularly harmful to patients because vascular lesions appear earlier, are more diffuse, and usually distally located, making their surgical treatment less effective [9–12]. Critical limb ischemia (CLI) is much more frequent in patients with DM who have an almost twice higher risk of amputations compared to people without diabetes [11, 13, 14]. Also, the mortality rate after amputations in this group is very high at 50–74% in 5-year all-cause mortality [15].

Concomitant peripheral neuropathy, one of the chronic microcomplications of diabetes, may mask typical limb ischemia symptoms for years, promoting disease progression and delaying proper treatment [9]. The project published by Nichols suggests that diabetic peripheral neuropathy (DPN) and PAD are strongly related and that DPN may often precede PAD [16]. On the other hand, arteria stenosis aggravates DPN [16]; thus, the relation seems to be bidirectional.

The first, noncharacteristic symptoms of lower limb ischemia, such as cramps, numbness, or hypersensitivity to cold (Fontaine stage I) [17], can be confused with sensory neuropathy. The most common symptom that patients present is claudication (Fontaine classification stage II). This unpleasant symptom can also be masked by concomitant neuropathy or confused with musculoskeletal problems, which are also often found in the obese population of patients with T2DM. As a result, these patients often visit doctors when the disease is advanced and rest pain and/or necrosis (Fontaine stage III and IV, respectively) appears, which requires surgical intervention and is the cause of the most common, nontraumatic amputations in the world [17–19]. PAD prevalence in DM patients is difficult to accurately estimate because it may be asymptomatic or misdiagnosed for a long time in a large proportion of patients [20, 21].

These unfavorable circumstances make interdisciplinary cooperation with all possible conservative treatment forms, including rehabilitation, the key to effective PAD treatment in patients with diabetes. The undertaken actions should be focused on how to slow the disease progression and stimulate the development of collateral circulation, which can cover the insufficient perfusion caused by the main vessel's trunk occlusion or its important stenosis.

This article is aimed at presenting the current place and possibilities of physiotherapeutic management in the course of PAD in patients with DM. This management is dedicated to patients with claudication and those with critical limb ischemia that can and cannot be operated on. Interventions are multistep and lifelong, just as the disease is chronic. They are often highly individualized due to multiple comorbidities that may, like some used medications, limit some forms of physiotherapy or necessitate their modification.

Rehabilitation consists of a number of consecutive but overlapping stages: assessment of the clinical condition at baseline and during the intervention, physiotherapy (individually tailored to the patient's condition and capacity), optimization of pharmacological treatment, control of modifiable risk factors (e.g., smoking cessation, education on healthy nutrition), foot care, education of patients and their families, and psychotherapy [22–25]. It requires close cooperation between the patient and the treatment team composed of an angiologist, diabetologist, vascular surgeon, physiotherapist, nurse, dietician, psychotherapist, and often a prosthetist.

2. Kinesitherapy

Kinesitherapy is recommended as the first-line treatment for PAD and T2DM, playing a therapeutic role in both diseases. This role comes down to a beneficial modification of known cardiovascular risk factors that can be influenced by the physical effort and almost immediately found, including hypertension, lipid disorders, obesity, and carbohydrates disorders. Additionally, patients benefit from exercise in many ways, often not immediately perceived, such as reduction of inflammation (underlying atherosclerotic process and aggravated in carbohydrate metabolism disorders) or increase in nitric oxide release, the most important vasodilator substance in the human body [12, 26, 27]. However, the patient with diabetes requires special involvement at the stage of exercise planning.

2.1. Planning Physical Effort in Peripheral Artery Disease in Patients with Type II Diabetes Mellitus. Conservative treatment in patients with DM complicated by PAD does not significantly differ from the recommended one in the population without DM; however, special emphasis is placed on glycemic control and the resulting limitations.

American Diabetes Association (ADA) guidance for individuals with DM focuses on glucose control with recommended hemoglobin A1c (HbA1c) < 7%, or close to 6%, to reduce the risk of complications. Both hyperglycemia (>250–300 mg%), as well as hypoglycemia (<100 mg%), should be generally avoided, but mainly before the patient starts physical activity. It protects individuals from ketoacidosis or uncontrolled lowering of the glucose during and after the exercise [28]. Moderate to vigorous aerobic exercise (≥30 min, 5–7 days/week) combined with anaerobic exercise (≥3 ×/week) is recommended to achieve better glycemic control. [29]. It affects both the modification of glycemic values [30] (both types of effort) and is a part of walking training (the aerobic one). Regular exercise modifies insulin effect in the muscles and liver. Aerobic exercise increases muscle glucose uptake up to fivefold in an insulin-independent manner. After physical training, glucose uptake remains elevated in insulin-independent (~2 h) and insulin-dependent (up to 48 h) mechanisms if exercise is prolonged (48), which is linked with muscle glycogen pool restoration [31, 32]. On the one hand, this is a desirable effect, but on the other hand, it can promote hypoglycemia even hours after the activity cessation in some situations. Depending on the diabetes treatment, it is, therefore, essential to discuss the risk of hypoglycemia with the patient, as this is especially the case in patients treated with insulin or sulfonylurea [29]. In this issue, the contact between the team's members is critical because the lack of understanding of the mechanisms responsible for hypoglycemia may discourage patients from participating in exercise therapy from the very beginning.

Before physical training, individuals with DM should be screened for cardiovascular complications. It is part of safety features and arises from the common coexistence of the atheromatic lesions within other locations, mainly coronary circulation, together with the possibility of the autonomic neuropathy responsible for the so-called silent ischemia. Some medications (e.g., beta-blockers), often used for comorbid conditions, such as heart disease or hypertension, may limit exercise capacity through their effects on heart rate; other medicines can increase the risk of local bleeding (antiplatelet or anticoagulant medications) after possible injury,

which should be monitored and information provided to the patients and their doctors.

Also, assessment of other chronic microvascular complications, including diabetic retinopathy, diabetic nephropathy, and peripheral neuropathy, may translate into recommendations for physical activity for patients with diabetes in general and those with coexisting limb ischemia.

According to the recommendations, when planning vascular rehabilitation in patients with DM, a typical blood circulation assessment (physical examination, additional tests) is necessary. Estimation of the claudication distance (initial and absolute) should be performed on a treadmill or, in case of limited possibilities, as a corridor test [29, 33]. Performing the test informs not only therapists of the clinical severity of the disease but also serves as an introduction to walking training education. It is also often used to assess the objective parameter of the postexercise ankle-brachial index (ABI) [33]. It should be taken into account that the sensitivity of resting ABI values is much lower in patients with DM [12] than in the general population. It is associated with an increased risk of arterial stiffness and microcirculation abnormalities [34]. If vascular sclerosis is not confirmed, ischemia occurs when the index value is ≤0.9. The progressively lowering value is associated with greater functional limitation and severe ischemia diagnosis when ABI is below 0.4–0.5 [33].

Mehta et al. [35] presented in 2020 the advantages and drawbacks of postexercise ABI based on a clinical case. The authors describe the mismatch between the recommended criteria for an abnormal postexercise ABI value and a low sensitivity of postexercise ankle systolic pressure decrease of more than 30 mmHg for diagnosing PAD. The authors suggest that postexercise ABI decline of more than 20% or postexercise ankle pressure decrease of more than 30 mmHg can establish PAD diagnosis and should prompt initiation of appropriate medical management [35].

In addition, to the posttest ABI assessment, if resting ABI is not possible to be interpreted, supplemental physiological testing studies may be indicated, including toe-brachial index (TBI), skin perfusion pressure, or transcutaneous oxygen pressure [33].

The exercise tests are also performed to assess and monitor the result of conservative treatment, e.g., six months into the rehabilitation program and the vascular procedure effectiveness [18].

2.2. Supervised Exercise Walking Training (SET). The effect of diabetes on daily physical activity levels in patients with PAD is poorly studied, and current guidelines do not specify individual rehabilitation management recommendations for patients with PAD and diabetes. A recent study [36] reported that patients with DM and intermittent claudication presented less physical activity and reduced their physical function more than those with PAD alone. It has been suggested that diabetes contributes to reduced blood volume expansion and impaired skeletal muscle oxygenation. Because physical activity can correct these above disturbances [37], patients with DM may benefit from physiotherapy even more than the general population. A systematic review published in 2017 by Hageman et al. [38] summarized the literature dedicated to the impact of diabetes, as a comorbid disease, in patients with intermittent claudication (IC) on the effects of supervised exercise training. The review included randomized and nonrandomized studies with walking abilities, after SET, assessment in patients at 2nd level of the Fontaine's score. Considered outcome measures were maximal (absolute), pain-free (initial), and functional walking distance (MWD, PFWD, and FWD). The vast majority of the studies have confirmed improved walking performance in both patients with DM and patients without DM. Given the knowledge currently available, supervised interval treadmill training has a well-established role as a first-line therapy in the treatment program for patients with claudication [39, 40], including those with diabetes [12]. Improvements can be expected in both: PFWD (by 128 meters on average) and MWD (by 180 meters on average) [41]. The principles of supervised exercise, based on the 2007 TASC II guidelines [28], are regulated and updated by the European Society of Cardiology (ESC) guidelines prepared in collaboration with the European Society for Vascular Surgery (ESVS) [42]. According to the recommendations, exercise session should last from 30–60 minutes with rest breaks, just before the absolute distance of claudication reaching (the patient marches on moderate pain—so-called submaximal effort) [28, 33, 40, 42]. After walking cessation, it should be resumed once the pain subsides, which usually takes no more than 5 minutes. Sessions should be conducted 3–5 times per week for a minimum of 3–6 months [28, 33, 40, 42, 43], but generally should a lifelong procedure. Explaining the principles of this activity to the patient, including the acceptance of experiencing slight pain while walking, is essential for both the patient's psychological well-being and treatment outcomes [20]. Patient acceptance of the pain while walking with the understanding of its nonharmful character is crucial for proper implementation of the rehabilitation program but often difficult to achieve. It is because patients perceive ischemic pain as a contraindication to continuing exercise, extrapolating this situation from the rules surrounding physical activity in heart disease. The risk of coexisting neuropathy (including hypoesthesia) makes education about hygiene and proper footwear a unique element of the rehabilitation process. After each session, the patients should carefully examine the feet (on their own or with the help of another person) in order to detect injuries, calluses, abrasions, or areas indicating mismatched footwear (e.g., redness). The patients should remember to drink enough fluids during exercise to avoid overheating and dehydration [44–47].

In summary, SET is considered the gold standard regardless of the coexistence of DM but requires special attention and awareness due to more limitations resulting from this additional disease.

2.3. Nordic Pole Walking Exercise. In recent years, Nordic pole walking (NPW) has become a new, popular, and recommended form of training for cardiovascular disease patients. This technique engages arms and trunk muscles, significantly relieving the load on the lower limbs during walking [48, 49]. The beneficial effect of NPW on extending the distance of

claudication was demonstrated in a study by Oakley et al. [50]. The authors emphasized its additional qualities as NPW might also be a helpful exercise strategy for improving the cardiovascular fitness of patients with intermittent claudication. It is of great importance as cardiac complications are the leading cause of death in this group [51]. Other reports on regular training with NPW in patients with PAD have confirmed that NPW training generally improved exercise tolerance, perceived quality of life (QoL), and decreased symptoms of claudication pain during walking [52–54]. Bulinska et al. [55] compared the efficacy of NPW training with traditional treadmill training on PFWD and MWD in patients with PAD. Rehabilitation sessions were performed three times per week for three months. The authors show that the MWD increased significantly more after an NPW program compared to walking without poles. Thus, studies confirm that NPW is at least as effective as traditional walking training when used in the rehabilitation of patients with PAD [55]. Additionally, the significant amount of muscles involved during this activity may also promote a better glycemic effect, and the method of performing this exercise makes patients feel much more secure.

2.4. Cycloergometer Exercise. Exercise on a bicycle ergometer is an excellent alternative for patients with DM complicated by PAD, to whom treadmill walking exercises are particularly uncomfortable or difficult [47]. This type of bicycle does not overload limb joints and spine as much as marching, which is favorably perceived by exercise participants, especially the elderly and obese. In addition, stationary cycling is beneficial for safety reasons (e.g., dizziness) and makes exercise independent of the weather. Before training on a bicycle ergometer, the patient should be instructed individually on the appropriate exercise load and the rules for performing the exercise. The patient should rest the front part of the foot on the bicycle pedal, which allows for a greater load on the distal limb muscles. The exercise should be performed daily, and the distance covered by the patient should be about 10 km [56]. The study conducted by Haga et al. evaluated the effectiveness of a three-month supervised bicycle program in improving walking abilities in patients with PAD. Intermittent claudication showed that bicycle exercise improved the MWD and QoL in patients with PAD. This training engages much more distal, below-knee muscles than the proximal ones, which is especially beneficial for patients with DM due to more common peripheral vessel stenosis in this group. The results showed that bicycling might be as useful as walking in patients with PAD [57].

2.5. Resistance Training. Current guidelines recommend resistance, anaerobic exercise as complementary training for patients with DM [33]. Dynamic resistance exercise, in particular, should be recommended for physically inactive individuals with chronic comorbid conditions like obesity, arthritis, and balance disorders, as they make it difficult to use other abovementioned traditional training. Resistance exercise increases limb muscle mass and strength [58] which translates into improved glucose metabolism. In addition, greater muscle mass promotes better balance and is a prerequisite for proper aerobic exercise, where symmetrical muscle work is required. However, this symmetry is often disturbed by sarcopenia, which results from both ischemia and involuntary relieving of the affected limb. Rebuilding muscle mass during the first months of therapy is, therefore, a necessary element of rehabilitation in this group of patients. Resistance training is well tolerated because, usually, it does not cause chronic pain. The ESC guidelines [12] emphasize that the combination of aerobic and anaerobic training is the most beneficial form of exercise for people with DM because of its strong, complex modifying effect on atherosclerotic risk factors such as hyperglycemia, lipid disturbances, and hypercoagulability, which characterize people with metabolic disturbances typical for insulin resistance. It is recommended that resistance training should be performed for approximately 15 minutes/3 days per week at 30–50% of maximum muscle strength followed by the rest. The maximum load should be determined before the training session. Exercises to improve flexibility and balance should be added to the above training forms, especially in patients with DM [12].

The review conducted by Machado et al. assessed the effects of combined aerobic and resistance exercise programs compared to the isolated aerobic exercise and the usual care in patients with intermittent claudication on walking performance [59]. Improvement was noted, as combined exercise and isolated aerobic exercise improved the claudication PFWD from 11 to 396% and 30 to 422%, respectively, and the absolute claudication distance from 81 to 197% and 53 to 121%. The authors emphasize that there is a strong need for randomized controlled trials to refine the strength of the effect of combining these activities in patients with PAD.

Despite the paucity of evidence regarding the effects of combining marching training with resistance training for patients with diabetes mellitus complicated by PAD, proposing combined exercise to this group of patients appears to be a reasonable and safe strategy to improve gait performance and modify cardiovascular risk factors in view of the basic knowledge relating to their mechanisms of action.

2.6. Particular Situations. In the aortic-iliac or femoral type of ischemia, patients can be additionally encouraged to perform exercises according to Horodynski's scheme (exercises of thigh and buttock muscles, e.g., squats). In the peripheral type of ischemia, Ratschow's and Buerger's exercises are recommended. These exercises are performed in the supine position with the provocation of extremity ischemia through extremity elevation, followed by forced passive congestion by lowering the lower limbs—similar rules are observed in upper extremity ischemia [60–62]. In patients at any stage of ischemia, including critical cases, which is a contraindication for walking training, the patients should be encouraged to perform individual rehabilitation program (e.g. respiratory, antithrombiotic, or/and upper extremity exercises). Patients with diabetes and PAD who cannot participate in supervised exercise sessions for many reasons should be advised to perform home-based exercise training (HBET) [47]. Collins et al. were the first to confirm the effectiveness of walking training, performed at home, in patients with DM complicated by PAD. In these patients, improvements

were noted in walking distance, gait speed, and quality of life [63]. According to the recommendations, HBET should be done 3 to 5 times a week, from 15 (initially) to 40–50 minutes. Unsupervised walking training requires patients to be adequately trained on the safety and correctness of performing the exercise. This guarantees the effectiveness of the exercise. Walking should be dynamic, rhythmic, and performed on a flat, moderately hard surface (e.g., park paths) following the principles of personal safety and exercise hygiene like during supervised sessions. Despite the high efficacy of unsupervised training in well-motivated patients, its effectiveness depends on systematic reeducation of the patients and its periodical monitoring with the necessary correction made by the specialist. Many authors suggest that effective home-based exercise programs for individuals suffering from diabetes complicated with PAD may require ongoing contact with a physiotherapist, at least during the first six months [24, 47, 56, 64], to consolidate good habits in patients and to confirm how to perform marching exercises well. A study published in April 2021 by McDermott et al. identified the need for home-based exercise in patients with PAD and demonstrated the higher effectiveness of high intensity of these exercises [65]. The effectiveness of home exercise therapy was also confirmed in a study by Fukaya et al. [66]. The role of home-based exercise is emphasized in situations such as the current pandemic, where lockdowns have significantly reduced the use of structured forms of rehabilitation.

It should be stressed that rehabilitation is also an introduction (so-called prehabilitation) [67] and a continuation of surgical treatment. It should be good practice to admit patients to the surgical ward 2–3 days prior to vascular surgery for laboratory procedure and enable their education in postoperative rehabilitation. According to the 2019 guidelines on peripheral arterial disease by the European Journal of Vascular Medicine, rehabilitation should be implemented from the 14th day of discharge after the surgery [39]. Pandey et al. in 2017 [68] published an interesting meta-analysis of randomized, controlled trials to show the efficacy of initial endovascular treatment with and without supervised exercise training in patients with claudication. 7Change in PFWD, MWD, resting ABI was recorded to assess the risk of revascularization or amputations. First of all, the results underlined a known and obvious fact that endovascular procedure reinforced with supervised walking training was more effective than SET alone (improvement in total MWD, ABI, and reduction in the risk of revascularization or amputation). However, even more interesting was another analysis, which revealed that the use of invasive methods alone without complementary rehabilitation does not produce the expected improvement in functional capacity [68]. Thus, finally, the study stressed the role and strength of comprehensive treatment applied together.

3. Contraindications for Kinesitherapy

Exercise should be considered a part of the therapeutic management of patients with DM complicated by PAD. However, there are exceptional situations where they must be restricted. Exercise is contraindicated in patients with acute coronary heart disease until the patient's condition stabilizes, which takes approximately five days [69]. Other important exercising contraindications include advanced heart failure and rest dyspnea of any origin, recent myocardial infarction or active signs of ischemia in electrocardiogram (unstable angina), complete heart block, myocarditis, endocarditis, pericarditis, left ventricular outflow tract obstruction, pleuritis, pericarditis, and if systolic blood pressure falls by 30% of baseline during exercise. When blood pressure exceeds >160/100 mmHg, the exercise should be periodically discontinued [69–71]. Contraindications are also common in rheumatoid arthritis and osteoarthritis when there is acute inflammation or pain during exercising. There are several considerations that are important and specific for patients with diabetes. As was mentioned, significant hyperglycemia, mainly with a positive urine test for ketones and too low glucose (in patients treated with insulin or sulfonylureas), constitutes a contraindication [29]. Also, chronic diabetic complications like proliferative retinopathy and/or nephropathy should be considered an indication for an individualized approach. A condition that is specific to diabetes and requires special surveillance is the presence of abnormalities (deformities, abnormal location of the pressure on the sole) found on the patient's feet, as they promote the generation of local ulcers [45]. Providing the patient with special pressure-relieving insoles or special shoes and choosing exercises that reduce the chance of ulceration in the so-called high-risk foot (e.g., a cycloergometer with modification of the plantar support point on the pedal) gives a chance for safe and satisfying exercise.

4. How Does It Work? The Molecular and Biochemical Aspect of Exercise Training Offered to Patients with Pad Related to Diabetes Mellitus

Currently, despite the passage of many years from the introduction of the first principles of treatment for lower extremities atherosclerosis and despite significant advances in vascular surgery, physical activity remains an indispensable tool for improving limb blood supply [63]. It is achieved by activating many beneficial mechanisms, often not fully recognized, and modifying the most common risk factors that cannot be obtained with a surgical procedure [72–75]. The most important clinical effect is the improvement in claudication distance, but how do such beneficial changes occur? Vascular obstruction causes metabolic dysfunction at the skeletal muscle level. Chronic ischemia, along with the low level of physical activity, changes the phenotype in patients with PAD and results in decreased muscle tissue density, increases fat content, accelerates muscles cells apoptosis, reduces type I fibers, and reduces capillary density [72].

Many authors have shown that repetitive exercise improves hemorheology, thereby facilitating oxygen delivery to ischemic skeletal muscles [76–78]. It also improves the metabolism of the skeletal muscles and provides more economic mitochondrial energy production [72]. Exercise

training improves oxygen extraction and carnitine metabolism within the working muscles also [79]. The upregulation of endothelial nitric oxide synthase, which improves nitric oxide release, is stimulated by increased shear forces during the excessive blood flow in muscles when working out. This could explain vasodilatation [80–82].

This was proved as exercise decreased systemic markers of inflammation, including mentioned molecules [72], and ultimately improved endothelial function [73, 83].

5. Other Therapeutic Tools

5.1. Pulsatile Pneumatic Compression Therapy. Intermittent/-pulsatile pneumatic compression (IPC/PPC) appears to be a helpful adjunctive form of treatment for patients with PAD, including those with diabetes [84, 85]. Current findings related to this therapy indicate measurable effects in specific groups of patients [86]. IPC is based on transferring external pressure to the extremities by means of a pump that is periodically inflated with air or water. Pulsatile manner means that gradual compression applied to the legs to pressure value, usually close to the patient's systemic, diastolic one, is followed by the rapid deflation of the cuff. The compression result can be compared to the effect of fast walking, with no risk of pain or injury [87]. The procedure should be performed as often as possible (preferably daily) for about 2.5 h [62]. During the session, an increased arteriovenous pressure gradient reverses vasomotor paralysis, which secondarily increases nitric oxide release from endothelial cells, thus increasing vasodilation. Finally, perfusion is improved and, what is also very important, tissue edema can be reduced. Swelling often accompanies rest pain and results from patients holding their legs down for many hours to resolve the pain, but unfortunately causing constriction of small, mainly subcutaneous blood vessels that exacerbate the ischemia. For patients who are ineligible for surgical intervention due to contraindications and/or lack of technical feasibility, intermittent compression therapy may be associated with improved amputation-free time survival, less rest pain, and improved quality of life [87].

Alvarez et al. [88] evaluated the efficacy of treatment with high pressure (IPC) in subjects with symptomatic PAD or CLI symptoms.

It has been shown that this type of IPC promotes the healing of wounds and reduces associated chronic pain in subjects with CLI and improving walking distance in patients with intermittent claudiction (IC). The authors suggest that IPC is safe and effective and should be considered for patients who are not candidates for endovascular or surgical procedures.

IPC is a safe therapy that can be used both in hospital or outpatient conditions and, after appropriate patient training, also at home [86]. The use of the so-called circulation boot, which is a variation of the "soft" form of IPC, gives the opportunity of topical application of antibiotics or other substances improving ulcer healing [89, 90].

5.2. Physical Therapy. Physical therapy is recommended as adjunctive or the only treatment when there are contraindications for other methods [56, 91]. Patients with good glycemic control, without acidosis, and who do not present severe vascular complications can be qualified for physical therapy [91, 92]. The treatment effectiveness is determined by the mechanisms expected to lead to vasodilation and can present an analgesic and/or anti-inflammatory effect. The effect of physical stimuli on the improvement of tissue metabolism, peripheral nerve, and vascular function can help treat ulcers in patients with diabetic foot syndrome. Often, additional effects are achieved during treatment, including improvement in complaints resulting from comorbidities (e.g., osteoarthritis), which not only affects the patient's positive perception of the treatment but also helps to prepare the patient more effectively for physical exercise by reducing pain from causes other than ischemia [41, 56, 91, 93].

Physical therapy agents most commonly used to treat patients with DM and PAD include phototherapy with low-energy lasers and polarized light; magnetotherapy; electrotherapy with TENS currents, iontophoresis, longitudinal galvanization, diadynamic currents, electrostimulation; ultrasound; and heat treatments (local and general), short-wave diathermy, and shock wave [56, 91–96].

However, it is worth noting that due to quite frequent sensory failure present in diabetes, the application of currents or thermal treatments should be carefully considered to avoid burns [56].

Studies conducted so far [92, 96–101] have demonstrated the effectiveness of the abovementioned physical therapies in reducing the extent of ischemic foot ulcers and improving limb blood supply [92, 97–101] in individuals with DM.

However, it should be noted that not all studies so conclusively support the validity of physical therapy. In their multicenter, double-blind, randomized controlled trial, Ennis et al. did not confirm the effectiveness of ultrasound treatment on wound healing in patients with chronic diabetic foot ulcers [102]. Also, in a randomized crossover study conducted by Guirro et al., no statistical significance was found to support the short-wave diathermy treatment in a group of patients with a similar condition [96].

Of note, the role of complex therapy, understood as physiotherapy, is carried out in spa conditions. In addition to the possible coapplication of different types of supervised physical activity, behavioral education, and physical therapy procedures, the use of typical spa forms of therapy may be an additional benefit (e.g., mood therapy, water-based therapy). In patients with DM and chronic circulatory complications, health-resort treatment directed at improving blood supply to the tissues is recommended. Acid-carbonated water and gas baths, sulfide-sulfide baths, and whirlpool massage of the lower limbs increase skin flow and dilate blood vessels [94]. Mud paste packs, which dilate capillary vessels, are also used. A combination of the above agents can also be applied [103].

However, it should be emphasized that the current studies on the effectiveness of physical therapy methods and accompanying economic aspects are not exhaustive. Nevertheless, physical treatments and spa therapies seem to be an attractive alternative or supplement to the standard therapy

for selected individuals, especially those with no invasive treatment options [56].

5.3. Systemic Hyperbaric Oxygen Therapy (HBOT). The consistently unsatisfactory therapy results for critical limb ischemia have forced the search for adjunctive forms of treatment to surgery. One of the alternative or complementary methods is systemic hyperbaric oxygen therapy. Hyperbaric therapy involves placing the patient in a chamber where 100% oxygen is applied under increased pressure. The oxygen thus administered dissolves in the plasma, which allows its transport to the tissues with very poor perfusion. Hyperbaric oxygen therapy increases neutrophil killing ability, stimulates angiogenesis, and enhances fibroblast activity and collagen synthesis [104]. An absolute contraindication to the use of conjugated oxygen therapy is untreated pneumothorax and chemotherapy [105]. Data relating to the efficacy of HBOT are conflicting. While some authors do not indicate that this method significantly improves ischemic ulcer healing [106], others report the effectiveness of HBOT in treating the infected diabetic foot [104, 107, 108]. The last meta-analysis performed in January 2021 concludes that HBOT was associated with higher rates of diabetic foot ulcer healing and reduced rates of major amputation of the lower extremity. The authors suggest a great need for well-planned, sufficiently multicentric trials to assess the efficacy and safety of HBOT as an adjuvant treatment for diabetic foot ulcers [109].

In conclusion, HBOT is a rapidly growing branch of medicine. The use of this form of therapy to treat ischemic lesions in patients with diabetes requires further research. Nevertheless, HBOT should be considered an adjunctive or alternative part of treatment for patients with diabetic foot.

5.4. Lower Limb Offloading. In terms of physiotherapeutic management of patients with CLI, lower limb pressure relief is also indicated. It is recommended primarily for patients with neuropathic foot, but it also supports the treatment of ischemic ulcers. Among other things, weight-bearing helps to improve perfusion in the foot [28] and prevents damage to the foot by inappropriate footwear, especially if any deformation is present [110]. Different methods can achieve partial or complete pressure-relieving, i.e., shoe modification [111–113], individually tailored insole [114], podological treatment using individually tailored materials [110], also pelotics (protection of sensitive areas is achieved by absorption of pressure forces by a pressure-relieving material), taping [115], special plaster dressings [116, 117], but also use of crutches [118] or wheelchair in exceptional situations. The choice of the method to offload the pressure on the sole depends on the location of the ulceration and its severity but also the patient's general condition, ability, and acceptance.

Discussing each method of pressure relief is beyond the scope of this paper. It is important to recognize that methods such as using crutches or a wheelchair are also ways for individuals after amputation to get around in the first few months after surgery (sometimes by patient choice or necessity, for the rest of their lives). In both cases, the patient's mobility is determined by upper limb muscle strength. The use of electric wheelchairs is still not standard in many countries; thus, the patient's condition and upper extremity strength play a crucial role in an individual's independence. What is more, mobilizing the upper limb muscles improves overall patient function.

Technically, using a wheelchair is easier than walking on crutches. However, crutches allow the patient to get to places not available when using a wheelchair. The crutch phase, because of the difficulties encountered by the person, should be an important part of the rehabilitation process to prepare the patient for elective limb amputation [119, 120]. This elective procedure gives the medical team time to improve the patient's dynamic parameters of the limbs and trunk and thus build better performance of daily living activity after surgery. A significant effect of exercise should also maintain or even increase the joints' range of motion.

Bearing in mind the higher risk of critical limb ischemia with a higher rate of amputation in patients with diabetes, it is necessary to incorporate exercises of the shoulder girdle and free part of the upper extremity muscles in patients' rehabilitation programs to protect them from future disability.

6. Conclusions

Unfortunately, despite the proven and essential role of different forms of kinesitherapy in walking ability improvement, there is still too little knowledge about the impact of physical therapy, e.g., on wound healing or ischemic pain relief. Our faith in modern medicine procedures slowed down the studies in this field and uncovered many aspects that require further research. With the growing number of comorbidities, including diabetes and atheromatosis, the aging population makes rehabilitation the key to successful and optional treatment. The population cannot always be treated with the usual treatment options, and the recommendations for rehabilitation based on evidence medicine are strongly needed. However, the results of the available study give us the opportunity to develop comprehensive therapy, including rehabilitation.

Conflicts of Interest

Two of the authors of the paper (K.H. and K.B.) are employees of the same department as the main editor.

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Review Article

Pain Management in People with Diabetes-Related Chronic Limb-Threatening Ischemia

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Management of neuropathic pain in people with diabetes has been widely investigated. However, little attention was paid to address ischemic-related pain in patients with diabetes mellitus who suffered from chronic limb-threatening ischemia (CLTI), the end stage of lower extremity arterial disease (LEAD). Pain management has a tremendous influence on patients' quality of life and prognosis. Poor management of this type of pain owing to the lack of full understanding undermines patients' physical and mental quality of life, which often results in a grim prognosis, such as depression, myocardial infarction, lower limb amputation, and even mortality. In the present article, we review the current strategy in the pain management of diabetes-related CLTI. The endovascular therapy, pharmacological therapies, and other optional methods could be selected following comprehensive assessments to mitigate ischemic-related pain, in line with our current clinical practice. It is very important for clinicians and patients to strengthen the understanding and build intervention strategy in ischemic pain management and possible adverse consequence.

1. Introduction

Lower extremity arterial disease (LEAD) in diabetes is a leading cause of limb loss and has a profoundly negative impact on quality of life and early mortality [1]. Although intermittent claudication (IC) is considered to be the early symptom in patients with LEAD, it could be relieved by exercise, pharmacotherapy, and quitting smoking [2]. By contrast, critical limb ischemia (CLI) represents the end-stage manifestation of LEAD, with a major amputation rate of 30%, mortality rate of 25%, and chronic pain of 20% at one year [3, 4].

Although the pain is an important issue for most patients with CLI, it is often poorly managed and mismanaged [5]. Many individuals with LEAD not only have a higher amputation rate and mortality but also experience ischemic pain [6–8]. It has been widely established that coronary artery disease (CAD) and diabetes mellitus (DM) are among the prevailing comorbidities in patients with peripheral arterial disease (PAD). However, CLTI is observed to have higher mortality rate than symptomatic CAD [9].

Moreover, ischemic ulcers carried higher mortality risk than neuropathic ulcers in patients with DM, although neuropathic ulcers induce considerable morbidity than ischemic ulcers [10]. In addition, LEAD independently increases the risk of diabetes-related anxiety and depression with a negative attitude to treatment, which often leads to poor healing and amputation [11, 12].

Presently, no randomized clinical trial has been conducted, and no specific practice recommendation has been provided in the management of ischemic pain in patients with CLI [5]. It is difficult to conduct a systematic review and meta-analysis because widespread reviews of the literature or randomized controlled trials focused on pain management in CLI are scarce, especially in people with

diabetes. The timing and means of the good treatment protocol for CLI patients are very important to the patients because they often determine the success rate of limb salvage.

Therefore, we intend to discuss the current therapeutic approach for the management of ischemic-related pain in patients with diabetes-related CLTI through our clinical cases. The purpose of this study was to summarize different interventions available for the management of such condition, including the acceptable option for limb salvage with endovascular therapy and palliative care with pharmacotherapies in patients with CLTI.

2. Definition of CLTI (Formerly Known as CLI)

Despite the first definition of CLI being published in 1982, the discussion remains open about the hemodynamic criteria [13]. The emerging new definition of chronic limb-threatening ischemia (CLTI) is mainly characterized by rest pain, with or without skin ulcer or gangrene, which has replaced the term CLI in recent guidelines [5, 14]. CLTI is defined as "the presence of ischemic chronic rest pain (>2 weeks) typically in the forefoot with or without ischemic lesions or gangrene due to arterial occlusive disease" [15]. A recent position statement released by the European Society of Vascular Medicine suggests the inclusion of nonhealing leg ulceration of other origin into the definition of CLTI due to their poor prognosis and to consider the impact of frailty on adverse outcome [16].

3. Epidemiology of Diabetes-Related CLTI

It is estimated that up to 1 in 10 patients with LEAD has CLTI. The natural history of CTLI is of unpredictable nature and variable. Progression of CLTI from asymptomatic LEAD or IC has been estimated to be at least 5-10% within 5 years, while as much as 50% of patients diagnosed with CLTI may not even have previous history of LEAD [17]. The clinical presentation of LEAD is characteristically diffuse in distribution involving multilevel occlusions in distal vessels. In a pilot study, the prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes was 33% [18]. LEAD has also been associated with type 2 diabetes mellitus (T2DM). Diabetes mellitus is a major global epidemic; complications of diabetes including diabetic foot ulceration are increasing proportionally. In a large cohort study of patients with diabetic foot ulceration in China, the overall amputation rate among diabetic foot patients was up to 19.03% [19]. LEAD has been found to be 2-4 times more frequent in patients with T2DM compared to the general population [8]. It was estimated that the proportional attributable fraction of T2DM for incident LEAD was 14% in the USA [20].

Majority of patients with diabetes-related CLTI may present also with nonhealing ischemic ulcer to gangrene (Fontaine stage IV) [21]. In the ADVANCE trial, including 11,140 participants who had T2DM and PAD with a median duration of seven years, the baseline prevalence of LEAD was reported at 4.6% when LEAD was defined as chronic foot ulceration due to arterial insufficiency, need for peripheral revascularization, or lower-limb amputation of at least one toe [22]. Recent research has reported higher risk of mortality from coronary arterial disease (CAD) in long-term follow-up after retrograde recanalization of chronic total occlusion (CTO) in patients with DM [23].

4. Pain Characteristic of Diabetes-Related CLTI

4.1. Different from Diabetic Neuropathy. Chronic ischemic pain is one of the most frequent causes of pain in the lower extremities [24]. In particular, the coexistence of diabetes is a significant predictor for the development of CLTI and nontraumatic amputation. Although the ischemic pain caused by CLTI has a significant neuropathic component [25, 26], there are some distinctions from those of painful diabetic neuropathy (PDN), not only in pathophysiology but also in characteristics of CLTI [27–29]. Diabetic neuropathy is a unique neurodegenerative disorder of the peripheral nervous system, of which approximately 30-50% of patients developed neuropathic pain [30]. The developing field of pain medicine has gradually revealed the pathogenesis of PDN [27]. New guidelines for the treatment of PDN using distinct classes of drugs have been issued because the pain is known to affect both the mental and physical wellbeing of patients [31]. However, the clinical characteristic of chronic ischemic pain in LEAD is diverse, ranging from asymptomatic to intermittent claudication, rest pain, nonhealing ulcers, and eventually gangrene. Both the pathophysiology and mechanism of ischemic pain remain unclear, but several mechanisms have been proposed: hemodynamic abnormalities, oxidative stress, and alterations in skeletal muscle metabolism [32]. Besides, the reduction in arterial perfusion in the affected limb leads to the accumulation of metabolites; increased acidity in the ischemic tissue and the onset of central sensitization are present in patients with CLTI [17].

The characteristic and clinical appearance of chronic ischemic pain in LEAD usually cover from nociceptive pain in patients with IC to predominantly neuropathic pain in patients with CLTI. It has been shown that questionnaires (VAS, NPSI, S-LANSS, PDI, SF-MPQ) might be a helpful tool to investigate and diagnose ischemic pain [26].

4.2. Different from Cancer. Previous studies have indicated that persons with diabetic lower extremity complications have 5-year mortality rates similar to many common types of cancer [33]. The impact on quality of life by poor pain management in patients with CLTI is comparable to advanced cancer patients. It is well known that managing pain is a key part of cancer treatment, and the analgesic framework ladder established by the World Health Organization (WHO) has been used to guide clinicians through a systematic approach for many years [34]. The analgesic ladder consists of a stepwise approach which includes the use of some analgesic drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids, and strong opioids and optional nonpharmacologic management in treating cancer pain. The effectiveness of this recommendation is confirmed in a majority of patients with cancer pain. The next question is whether a clinician can adopt this framework in the mitigation of pain for patients with

diabetes-related CLTI. To the best of our knowledge, there is an ongoing debate about whether these guidelines remain the optimal pain management in all patients which encompasses persons with diabetic lower extremity complications.

5. Intervention of Pain Management in CLTI

5.1. Endovascular Therapy. In recent years, three leading vascular societies including the European Society for Vascular Surgery, the Society for Vascular Surgery, and the World Federation of Vascular Societies were determined to launch the Global Vascular Guidelines (GVS) in the effort to address the appropriate management of CLTI. Successful revascularization in CLTI, particularly in patients with tissue loss, nearly always requires reperfusion to the foot to promote wound healing and pain relief. Once the clinical manifestations of CLTI such as rest pain, ischemic ulceration, or gangrene have developed, the choice of the intervention such as balloon angioplasty, stenting, and surgical revascularization should be considered in these patients [2]. Moreover, patients who had substantial tissue loss on the background of diabetes-related CLTI will require rapid revascularization within 2 weeks from the first evaluation to in order to preserve the affected limb [35]. The following case presentations elaborate on our successful efforts in pain management and limb salvage in patients presented with tissue loss from underlying ulcerations secondary to diabetes-related CLTI.

A 68-year-old female with T2DM was admitted to the hospital with a 2-month history of progressing pain and redness in her right foot. She presented a 14-day history of worsening symptoms, especially in the big toe. Physical examination revealed a necrotic slough over the apex of the right hallux (Figure 1(a)), skin temperature was unremarkable, and pedal pulses were nonpalpable. The ankle-brachial index (ABI) was 0.4. The wound measured as 1.5 cm × 1.0 cm tissue loss without signs of bleeding (Figure 1(a)). Standard medical treatments including antibiotics were administered, blood glucose control was optimized, and peripheral circulation was improved. Analgesic medications such as ibuprofen plus codeine tablets (up to 2 tablets every 4 hours but not take more than 6 tablets in 24 hours), tramadol hydrochloride sustained release tablets, and intramuscular tramadol injection (100 mg, till a maximum of 400 mg per 24 h) were administered when necessary. However, the pain relief did not seem to be adequate, especially at night. Angiography indicated occlusion at the right anterior tibiofibular artery and segmental stenosis of the posterior tibial artery (Figure 1(b)). She underwent balloon angioplasty from the right dorsal artery to the posterior tibial artery, and intraoperative angiography showed satisfactory lumen diameter (Figure 1(c)). After 1 month, her wound recovered and the pain subsided (Figure 1(d)).

The diagnosis of CLTI was made on background of clinical symptoms of ischemic rest pain and nonhealing ulceration over two weeks, in conjunction with perfusion studies of the lower limb such as ABI and angiography. The learning point from this case is early revascularization, and appropriate analgesic medication could be an effective treatment to achieve adequate pain relief and limb salvage. This case study exemplifies the importance of revascularization in the management of pain resulted by diabetes-related CLTI.

Although revascularization strategy has been emphasized in the treatment of CLTI, the adequacy of pain management is entirely based on the drug of choice. A recent systematic review reported pharmacological therapies for the management of ischemic pain in patients with nonsalvageable CLTI [32]. Six studies were identified from 792 studies that met full inclusion criteria, and evaluated the use of intravenous lidocaine [36], oral gabapentin [37], intravenous ketamine [38, 39], and the combination of transdermal buprenorphine and epidural morphine/ropivacaine infusion [40, 41]. They found that all studies had shown an improvement in severity of ischemia pain in CLTI but with varying side effects. Therefore, no pharmacological agents can be recommended in this case because of the complex pathophysiology of pain in CLTI and limited clinical evidence [32]. Importantly, clinicians and patients should be aware of the consequences of pain syndrome in diabetes and the profound progression that can occur in the face of an ischemic limb with concomitant neuropathy masking symptoms. In another example, we present a case of progressive gangrene without a previous history of LEAD and the development of rest pain, all of which have been largely disparaged by the patient until the lower limb amputation has to be considered.

A 69-year-old man with T2DM presented to our emergency department for sepsis related with the left foot. The patient had a 3-month history of a progressive ischemic lesion on his left foot, starting from mild cyanosis, nonhealing arterial ulcer to gangrene. The patient's daughter meticulously photographed the course of the lesion over 81 days (Figure 2(a), image courtesy of the patient's family). The patient has been plagued by the progressive ischemic pain over 3 months, from the tolerable rest pain to the subsequent persistent severe pain. Initial clinical presentations were signs of toes turning cyanosed with accompanying symptoms of feeling cold in his left lower limbs cold and occasional tenderness during ambulation. As the symptom was not evident, the patient paid no attention (Day 1 in Figure 2(a)). Surprisingly, after a few days, his fifth toe became gangrenous and nonhealing skin ulcer occurred on his left external ankle region (Days 18 to 21 in Figure 2(a)). At the same time, symptoms of rest pains and IC have also emerged. The pain is now characterized as a constant burning sensation or numbness in the ankle or foot in the absence of activity. He scored 4 out of 11 points on the numerical rating scale (NRS) [42]. Yet, he refused endovascular intervention or amputation of nonviable fifth toe but agreed on pain-relief medications. Unfortunately, his left foot gangrene progressed gradually upon returning home (Days 39 to 65 in Figure 2(a)). Tissue loss in the foot ranged from small ulcer to widespread gangrene. During this period, though the pain was aggravated but has been well managed by a combination of oral analgesics including acetaminophen (500 mg, pills, 2 g per 24 h) and other NSAIDs. Once again, he disparages the seriousness of the condition and had no desire to seek medical assistance. As such, we did not have an opportunity to treat until the condition was life-threating. On examination, he had profound gangrene of the left foot (Day 81 in

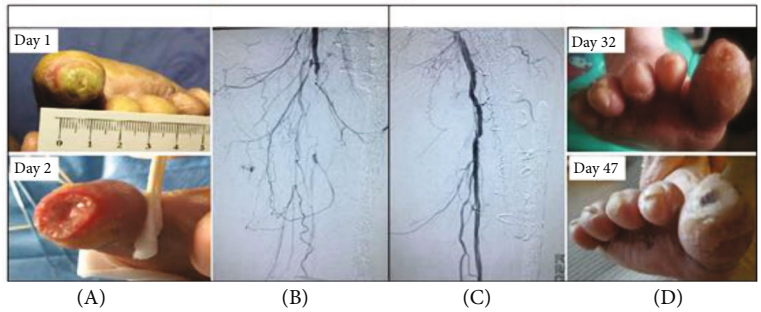

Figure 1: Lower limb salvage with revascularization in diabetic chronic limb-threatening ischemia.

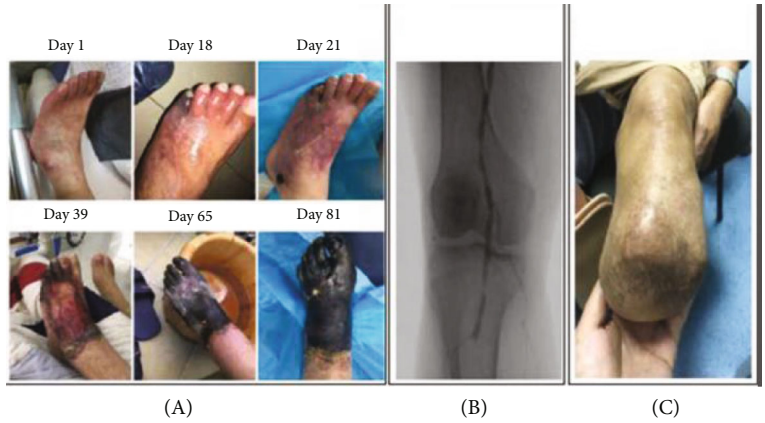

Figure 2: Amputation and endovascular therapy in diabetic lower limb gangrene.

Figure 2(a)). Following fluid resuscitation and culture of wound secretion, he was treated with broad-spectrum empiric antibiotic agents. Simultaneously, he was prescribed opioid-based analgesics such as tramadol to relieve the unbearable pain. Although it was effective by oral administration initially, the patient subsequently had an intramuscular injection of tramadol. Angiography revealed partial stenosis of the femoral artery and complete occlusion of the infrapopliteal vessels in the left lower extremity (Figure 2(b)). Following endovascular intervention and below-knee amputation, no worsening of gangrene was observed and pain has resolved completely, with no recurrence during 9 months of follow-up (Figure 2(c)).

As the risk of amputation in a deteriorating diabetic foot ulcer is high, when open or endovascular intervention has failed or is not possible, pain management is essential to improve quality of life and disease prognosis. From this case, we can learn that early medical intervention is important to improve clinical outcomes of CLTI.

Peripheral angioplasty (PTA) has been established to be the first-choice revascularization procedure in diabetic patients with CLTI. However, there are cases of CLTI that are not considered suitable candidates of angiographies or revascularizations for various reasons [43]. Firstly, it has been shown that the frailty syndrome in patients with diabetes is considered to be associated with worse prognosis for patients undergoing revascularization [44]. Secondly, on the background of chronic total occlusions (CTOs), patients with COPD treated with retrograde endovascular recanalization is associated with higher mortality [45]. Recent research has revealed that gender has an effect on long-term clinical outcomes in patients with CTOs of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions (PVIs) [46]. Males tend to have an increased risk of repeated PVI in patients with CTOs of infrainguinal arteries which was previously treated with retrograde access [46]. Moreover, the patients with diabetes present a higher rate of binary restenosis and amputation at 2 years following peripheral transluminal angioplasty [47] and restenosis is evident in some patients within 5 years postoperatively [48]. The rate of restenosis after endovascular treatment may be associated with impaired glycemic control and dialysis [49].

On the other hand, several studies have demonstrated that wound care, as the only treatment for CLTI, can heal approximately 50% of wounds without revascularization [50, 51]. Therefore, to some extent, it is difficult for clinicians to make the challenging decision—whether or not to perform the revascularization to save the limbs. In order to determine which patients will require and would benefit from revascularization, risk stratification that is based on three major factors as follows, Wound, Ischemia, and foot Infection (WIfI), has been introduced by the Society for Vascular Surgery Lower Extremity Threatened Limb Classification System in

2014 [12, 52]. With the WIfI classification system, revascularization significantly reduced the risk of amputation [53, 54]. This risk stratification system has been validated in clinical studies which demonstrated the potential utility of WIfI score to predict 1-year major lower extremity amputation (LEA) risk [55]. Moreover, the research also showed that after revascularization, wound severity is most strongly associated with LEA risk. Therefore, the three risk factors including tissue loss, ischemia, and infection are suggested to be evaluated to reduce the risk of amputation [56].

Endovascular therapy has increasingly become the initial clinical option for the treatment of LEAD, especially for patients with CLTI. Some recent studies have compared the clinical outcomes between open reconstruction and endovascular therapy for CLTI. The BEST-CLI (Best Endovascular versus Best Surgical Therapy in patients with Critical Limb Ischemia) trial is a prospective, multicenter, multispecialty randomized controlled trial designed to compare the effectiveness of open and endovascular interventions for 2100 patients suffering from CLTI [57–59]. In the overall CLTI population, the 3-year amputation-free survival was not different between the two treatment strategies in today's real-world settings [60].

5.2. Pharmacological Therapies. The treatment for CLTI is aimed at relieving ischemic pain, healing ischemic ulcers, avoiding limb loss, improving life quality, and prolonging survival. For pain management in CLTI, guidelines usually recommend a tiered approach, with a "trade off" between benefits and harms [5, 61, 62]. As no optimal pharmacological therapy has been established, the management of ischemic pain is challenging in patients unsuitable for endovascular intervention or amputation surgery [32]. It is difficult for clinicians to evaluate the effectiveness of palliative approach to deal with pain when all other options for limb salvage such as revascularization, surgery, and pharmacotherapies are exhausted. It is highlighted that intravascular lesions may be further aggravated during palliative care inadvertently. For the patients with CLTI caused by diffuse vascular calcification occlusions, endovascular therapy is ineffective and analgesia treatment cannot improve the sort of pain.

Accordingly, palliative pain management as a component of a care plan or a care focus early in the course of chronic diseases has been emphasized by the WHO [63]. Many studies have been conducted to investigate the use of lidocaine, gabapentin, or ketamine, which may optimize neuropathic pain' however, the supporting evidence of their efficacy for CLTI is limited [32, 64]. A previous study has demonstrated that patients with recurrent or stable nonhealing foot wounds can benefit from integrated palliative care such as managing pain [65]. However, it is important to stress that there is little research evaluating the risks and benefits of integrating palliative care into usual diabetic foot care, although it is possible to make some clinically meaningful recommendations. Some analgesic drugs and vasoactive substance such as tapentadol prolonged release and pentoxifylline are used to reduce the severe chronic ischemic pain with LEAD [66, 67]. Propionyl-L-carnitine (PLC) can reduce analgesic consumption and pain perception [68]. In theory, opioid combination with NSAIDs is effective at reducing opioid requirements; however, there is insufficient evidence that they can mitigate opioid side effects [34]. Nevertheless, these patients will gradually require increasing high opioid dose use [69], although some local anesthetics such as bupivacaine when combined with morphine will provide better and longer analgesic for ischemic pain as compared with a local bupivacaine alone for the short term. However, they are not used for the long term owing to serious adverse effects and potential addiction [70]. There is inconclusive evidence for the long-term effectiveness and safety of prostanoids in patients with CLTI [71, 72]. Moreover, a Cochrane review found that intravenous naftidrofuryl for CLTI was ineffective in reducing the symptoms of CLTI [73]. Table 1 shows the pharmacological therapies related to ischemic pain management in patients with CLTI.

For CLTI in patients with diabetes, in addition to the use of antithrombotic, lipid-lowering, antihypertensive, and glycemic control drugs, smoking cessation, diet, exercise, and preventive foot care advice with customized diabetic footwear are particularly important in order to achieve a better prognosis and quality of life.

5.3. Rehabilitative, Surgical, and Cellular Treatments. Besides the pharmacotherapies, there are many other methods that have been suggested to improve the pain and decrease medication utilization in CLTI. For example, spinal cord stimulation can provide for improvement in pain and potentiate wound healing of ischemic ulcers [74, 75]. A noncontrolled study that enrolled 38 patients with CLTI shows that 94% of patients experience pain relief [76]. The other study revealed the effectiveness of peripheral nerve crushing (Smithwick operation) to relieve chronic pain in diabetic and ischemic foot ulcers [77]. Besides chemical lumbar sympathectomy as well as epidural blockade with bupivacaine and morphine, ozone autohemotherapy seems to show beneficial effects in CLTI with ulcerations [78]. Transcutaneous electrical stimulation (TES) appears to be a useful method superior to drug therapy in curing arterial circulatory disturbances of the lower extremities [79]. Moreover, percutaneous deep vein arterialization perhaps represents an alternative option for the treatment of no-option diabetic CLI. In a pilot study including seven patients with diabetic CLI, complete wound healing was achieved in 4 of 7 patients and 5 of 7 patients at 6 and 12 months, respectively [80]. On the other hand, regenerative medicine approaches (e.g., cell and gene therapies) for CLTI have not been well established due to the restriction to rigorously conduct a randomized clinical trial. Our previous studies suggested that stem cell therapies are promising in the treatment of CLTI [81–84]. A case of DFU with normal blood supply was successfully treated with autologous platelet-rich gel combined with bone marrow mesenchymal stem cell transplantation [85]. Collectively, all these methods seem to be effective in wound healing and pain relief. However, these novel technologies should be subject to rigorous evaluation as their mechanisms and long-term outcomes remain further researched, especially in the environment of diabetic CLTI.

Table 1: Summary of pharmacological therapies related to ischemic pain management in patients with CLTI.

Reference	Study design	Participants	Intervention	Control	Administration method	Baseline pain scores	Postintervention pain scores	Statistical difference	Adverse effects
Tedeschi et al. [66]	Observational cohort study	$n = 25$	Tapentadol prolonged release	None	Oral administration for 3 months	Mean NRS: 7.9 ± 1.2	Mean NRS: visit 2: 5.7 ± 1.9; visit 3: 3.9 ± 2.1; visit 4: 2.8 ± 2.3	$p < 0.01$	None
The European Study Group [67]	Prospective, randomized, double-blind, placebo-controlled, parallel-group, multicentre trial	$n = 314$ (157 intervention, 157 control)	Pentoxifylline solution: 600 mg in 500 ml of saline	Saline: 500 ml	Intravenous infusions twice a day for a maximum of 21 days	Number (%) of patients VAS median Pentoxifylline: 40 (25-60) Control: 40 (25-60)	Number (%) of patients VAS median Pentoxifylline: -22 (-42-0) Control: -6 (-30-5)	Pentoxifylline vs. control: $p < 0.001$ 95%	Gastrointestinal symptoms (pentoxifylline: 59 cases vs. control: 18 cases; $p < 0.0001$)
De Marchi et al. [68]	RCT	$n = 48$ (24 intervention, 24 control)	PLC solution: 600 mg in 250 ml of saline solution	Saline: 250 ml	Intravenous twice a day for 15 days	Mean VAS Intervention: 9.6 ± 0.4 Control: 9.5 ± 0.4	Mean VAS Intervention: 5.3 ± 1.2 Control: 8.8 ± 1.2	PLC vs. correspondent baseline: $p < 0.01$	None
Veroux et al. [71]	Open-label, nonrandomized study	$n = 56$ (group A: 25; group B: 31)	Iloprost: group A: a continuous 6-hour 0.5 to 2.0 ng/kg·min once daily; group B: 20 days at a mean dosage of 25 pg/d	None	Group A: IV infusion for at least 14 consecutive days; group B: a portable elastomeric infusion system	Group A: 16 Group B: 16	Number of complete pain relief Group A: 6 Group B: 11	Complete pain relief rate Group A: 6/16 (37.5) Group B: 11/16 (68.8)	Patients (40.0%) who experienced AEs. In group B, 2 of the 31 patients (6.5%) had hyperemia
Keskinbora and Aydinli [70]	RCT	$n = 46$ (32 bupivacaine alone, 14 bupivacaine plus morphine)	Bupivacaine plus morphine: 0.125% bupivacaine+10 mg morphine in 20 ml of saline	Bupivacaine alone: 0.125% bupivacaine in 20 ml of saline	Popliteal catheter consecutively	NRS scores (at rest) Bupivacaine alone: 9 ± 1; bupivacaine plus morphine: 9 ± 0.6; NRS scores (during activity) Bupivacaine alone: 9 ± 0.7 Bupivacaine plus morphine: 9 ± 0.7	NRS scores (at rest) Bupivacaine alone: 60 min: 1 ± 0.2; 8 h: 3 ± 1.1 ; 12 h: 3 ± 0.6 Bupivacaine plus morphine: 60 min: 1 ± 0.3; 8 h: 2 ± 0.7; 12 h: 2 ± 0.8 NRS scores (during activity) Bupivacaine	NRS scores (at rest) Bupivacaine alone: 60 min: $p < 0.0001$; 8 h: $p < 0.0001$; 12 h: $p < 0.0001$ Bupivacaine plus morphine: 60 min: $p < 0.0001$(vs. baseline); 8 h: $p < 0.0001$ (vs. baseline or vs. bupivacaine alone); 12 h: $p < 0.0001$ (vs. baseline or vs. bupivacaine alone) NRS scores (during activity) Bupivacaine alone: 60 min: $p < 0.0001$; 8 h: $p < 0.0001$;	Nausea in bupivacaine plus morphine: $p < 0.001$ (30% vs. 0%)

Table 1: Continued.

Reference	Study design	Participants	Intervention	Control	Administration method	Baseline pain scores	Postintervention pain scores	Statistical difference	Adverse effects
							alone: 60 min: 2 ± 0.1; 8 h: 4 ± 1.2; 12 h: 3 ± 0.6 Bupivacaine plus morphine: 60 min: 2 ± 0.2; 8 h: 2 ± 0.5; 12 h: 3 ± 0.6	12 h: $p < 0.0001$ Bupivacaine plus morphine: 60 min: $p < 0.0001$ (vs. baseline); 8 h: $p < 0.0001$ (vs. baseline or vs. bupivacaine alone); 12 h: $p < 0.0001$(vs. baseline or vs. bupivacaine alone)	

RCT: randomized controlled trial; CLI: chronic limb ischemia; PLC: propionyl-L-carnitine; VAS: visual analogue scale; NRS: numerical rating scale.

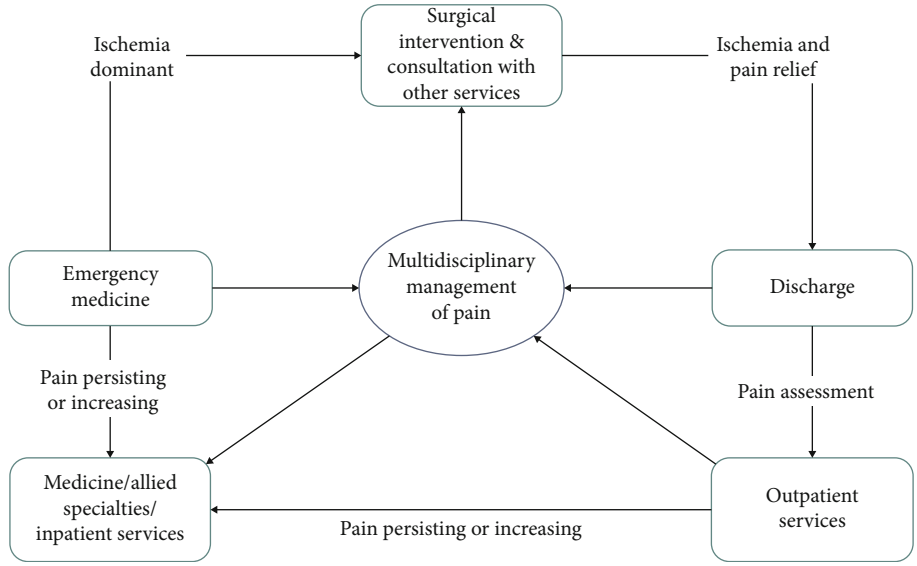

Figure 3: Management of ischemia pain with interdisciplinary team.

In summary, for patients with CLTI, endovascular therapy or surgical bypass surgery should be performed for vascular reconstruction as early as possible. Pharmacological treatments are the basis of the treatment of diabetic foot, which are suitable for patients with mild to moderate LEAD. They are primarily used to delay the development of the disease and improve the clinical symptoms and quality of life. In some cases, when the above interventions are unavailable or ineffective, some other methods such as spinal cord stimulation or lumber sympathectomy could be considered to relieve pain and to avoid complications.

Based on our experience, a multidisciplinary team approach to manage the chronic ischemic pain is vital, since different specialties have different therapeutic options for the treatment of chronic ischemic pain [86]. Moreover, no single specialty is able to manage all aspects of the patients with diabetic CLTI. At present, there may be a potential delay from the initial clinical symptoms of pain to the subsequent referral to the appropriate medical and surgical specialties. With increased participation of multidisciplinary specialties in the pain management of diabetic CLTI, the effort to salvage the lower limb has increased significantly, which may help to improve the poor prognosis. The pain management of CLTI in patients with T2DM requires a multidisciplinary team that is composed of endocrinologists, clinical pharmacists, vascular surgeons, and podiatric surgeons. Figure 3 illustrates a pain management team structure and the interdisciplinary components.

6. Conclusion

The management of pain in people with diabetes and CLTI remains a challenge. This is due to the complex pathophysiology of pain in CLTI, limited research base with pharmacological management, varying subjective feelings and severity of individuals, and varying degrees of pain relief for optional treatment approaches. For patients with ischemic pain caused by diabetes-related CLTI, the half-life of analgesia drug is short, so the effect is limited, and appropriate revascularization still remains an effective way to relieve pain and reduce the risk of amputation. Conservative therapy provides temporal pain relief but masks the progress of the ischemic foot and often leads to the disease deterioration. In addition, for ischemic diabetic foot with severe complications, all means may not be useful to avoid occurrence of adverse outcomes. Therefore, it is important for clinicians and patients to deepen their understanding of ischemic pain management and awareness of the possible adverse consequence as early as possible. Simultaneously, a multidisciplinary team approach to mitigate pain and reduce risk factors and comorbidities of CLTI is probably recommended. More efforts should be made to explore to formulate an effective intervention of relieving pain in patients with diabetic lower limb ischemia and to improve their quality of life avoiding the occurrence of adverse consequences.

Conflicts of Interest

The authors declare no competing interests in this work.

Authors' Contributions

Xiaoyan Jiang and Yi Yuan contributed equally to this work.

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Research Article

Different Patterns of Bacterial Species and Antibiotic Susceptibility in Diabetic Foot Syndrome with and without Coexistent Ischemia

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Aims. Infection in diabetic foot syndrome (DFS) represents serious medical problem, and the annual risk of DFS in diabetic patients is 2.5%. More than half of the patients with DFS have symptoms of extremity ischemia (peripheral arterial disease (PAD)). The aim of the present study was to analyze the frequency of particular bacterial strains in people with DFS, analyze the impact of arterial ischemia on the occurrence of a given pathogen, and evaluate the antibacterial treatment based on the results of bacterial culture. *Methods*. The analysis included 844 bacterial strains obtained from 291 patients with DFS hospitalized in the Department of Angiology in years 2016–2019. *Results*. The most common isolates were *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Nearly 20% of the species were found to have at least one resistance mechanism. In patients with PAD, Gram-negative species were isolated more commonly than in people without PAD. The most useful drugs in DFS in hospitalized patients are penicillins with beta-lactamase inhibitors, 3rd- to 5th-generation cephalosporins (with many exceptions), carbapenems, aminoglycosides, and tigecycline. *Conclusions*. Bacterial strains isolated from ischemic DFS are more resistant to commonly used antibacterial agents, i.e., penicillins (including penicillins with beta-lactamase inhibitors), cephalosporins (except for the 4th and 5th generations), glycopeptides, and linezolid. When planning treatment of hospitalized patients with DFS, the presence of ischemia in DFS should always be taken into consideration. It determines the occurrence of particular bacterial species and the choice of antibacterial agent and may determine the rate of treatment success.

1. Introduction

Diabetes mellitus is a social disease with the prevalence more than 5% that exerts a heavy burden on the healthcare system. One of the most common chronic complications of diabetes mellitus is diabetic foot syndrome (DFS)—defined as an infection, ulceration, and/or destruction of the foot in patients with diabetic neuropathy or peripheral arterial disease (PAD). The estimated global prevalence of DFS is 6.3% among patients with this disease [1]; it is also known that 20% of all diabetic patients require hospitalization because of DFS, and the annual risk of developing this complication is 2.5% [2].

One of the most serious problems faced by physicians treating patients with DFS is an introduction of appropriate empiric antibacterial therapy before the results of microbiological culture are collected and antibiogram is available. The aim of the present study was to analyze the frequency of particular bacterial strains in people with DFS, analyze the impact of arterial ischemia on the occurrence of a given pathogen, and evaluate the antibacterial treatment in this group of patients, taking into account the presence of PAD.

Table 1: Number of particular bacterial isolates in all patients with diabetic foot syndrome.

	Number of isolates	Percent
Staphylococcus aureus	211	25.00
Enterococcus faecalis	96	11.37
Enterobacter cloacae	66	7.82
Pseudomonas aeruginosa	58	6.87
Acinetobacter baumannii	54	6.40
Klebsiella pneumoniae	50	5.92
Escherichia coli	44	5.21
Proteus mirabilis	31	3.67
Streptococcus agalactiae	24	2.84
Proteus spp.	19	2.25
Enterococcus faecium	17	2.01
Morganella morganii	17	2.01
Finegoldia magna	12	1.42
Enterobacter aerogenes	9	1.07
Klebsiella oxytoca	9	1.07
Streptococcus mitis	9	1.07
Stenotrophomonas maltophilia	7	0.83
Veillonella spp.	6	0.71
Anaerococcus prevotii	5	0.59
Citrobacter freundii	5	0.59
Peptoniphilus asaccharolyticus	5	0.59
Streptococcus dysgalactiae	5	0.59
Bacteroides fragilis	4	0.47
Citrobacter braakii	4	0.47
Proteus vulgaris	4	0.47
Proteus penneri	4	0.47
Streptococcus pyogenes	4	0.47
Streptococcus constellatus	4	0.47
Clostridium sporogenes	3	0.36
Prevotella spp.	3	0.36
Providencia rettgeri	3	0.36
Serratia marcescens	3	0.36
Citrobacter koseri	3	0.36
Acinetobacter lwoffii	2	0.24
Actinomyces naeslundii	2	0.24
Bacteroides distasonis	2	0.24
Bifidobacterium spp.	2	0.24
Citrobacter youngae	2	0.24
Clostridium innocuum	2	0.24
Clostridium novyi	2	0.24
Corynebacterium striatum	2	0.24
Lactobacillus fermentum	2	0.24
Peptostreptococcus spp.	2	0.24
Prevotella melaninogenica	2	0.24
Propionibacterium acnes	2	0.24
Staphylococcus epidermidis	2	0.24
Alcaligenes denitrificans	1	0.12
Bacteroides uniformis	1	0.12
Clostridium subterminale	1	0.12
Clostridium perfringens	1	0.12
Clostridium hastiforme	1	0.12
Corynebacterium amycolatum	1	0.12
Fusobacterium necrophorum	1	0.12
Gemella morbillorum	1	0.12
Lactobacillus paracasei	1	0.12
Pseudomonas oleovorans	1	0.12
Peptostreptococcus anaerobius	1	0.12
Peptostreptococcus prevotii	1	0.12
Peptostreptococcus tetradius	1	0.12
Prevotella loescheii	1	0.12
Prevotella oris	1	0.12
Providencia stuartii	1	0.12
Staphylococcus hominis	1	0.12
Staphylococcus lugdunensis	1	0.12
Staphylococcus simulans	1	0.12
Streptococcus spp.	1	0.12

2. Material and Methods

The analysis included 291 patients hospitalized in the Angiology Clinic in the years 2016–2019 with a diagnosis of DFS with infection. According to IDSA guidelines, infection was diagnosed if two symptoms of inflammation (erythema, warmth, tenderness, pain, and induration) or purulent secretion were found [3]. In all the patients, a microbiological culture was performed using properly obtained material from ulceration (wound). The material was taken after rinsing the wound with 0.9% NaCl solution from the most profound obtainable tissues; tissue aspirates and material collected during surgical debridement or amputation were also cultured. The disk-diffusion method with paper discs impregnated with antibiotics at a specific concentration was used to determine the susceptibility of microorganisms to antibiotics and chemotherapeutics. The detailed protocol of the testing can be found in the literature [4]. The size of the inhibition zone around the disc indicates the susceptibility of the particular bacterial strain to the analyzed antibacterial agent.

The patients were classified as having ischemic DFS (if peripheral arterial disease (PAD) was present, irrespective of the presence of polyneuropathy) or as having nonischemic DFS (if peripheral arterial disease was absent and there was polyneuropathy). Polyneuropathy was diagnosed based on the patient's history and the results of physical examination including assessment of temperature (using Tip-Therm), touch (10 g monofilament), pinprick, vibration (128 Hz tuning fork), and reflexes (Achilles tendon reflex and knee reflex) [5]. If the results of neurological examination were not conclusive, electromyography and electroneurography were performed. The diagnosis of peripheral arterial disease (PAD) was established according to the current guidelines by means of accessory examinations, i.e., ankle-brachial

Table 2: Number of particular bacterial isolates in all patients with nonischemic diabetic foot syndrome.

	Number of isolates	Percent
Staphylococcus aureus MSS	88	14.47%
Enterococcus faecalis	48	7.89%
Pseudomonas aeruginosa	41	6.74%
Enterobacter cloacae	33	5.42%
Escherichia coli	32	5.26%
Staphylococcus aureus MRSA, MLSB	25	4.11%
Acinetobacter baumannii MDR	24	3.95%
Klebsiella pneumoniae	24	3.95%
Enterobacter cloacae ESBL	20	3.29%
Proteus mirabilis	17	2.80%
Staphylococcus aureus MSS, MLSB	17	2.80%
Proteus spp.	15	2.47%
Enterococcus faecalis HLAR	14	2.30%
Klebsiella pneumoniae ESBL	13	2.14%
Streptococcus agalactiae	12	1.97%
Staphylococcus aureus MRSA	12	1.97%
Morganella morganii	11	1.81%
Acinetobacter baumannii	10	1.64%
Finegoldia magna	10	1.64%
Klebsiella oxytoca	8	1.32%
Enterobacter aerogenes	8	1.32%
Streptococcus mitis	6	0.99%
Stenotrophomonas maltophilia	5	0.82%
Peptoniphilus asaccharolyticus	5	0.82%
Enterococcus faecium HLAR	5	0.82%
Enterococcus faecium	5	0.82%
Veillonella spp.	4	0.66%
Proteus penneri	4	0.66%
Escherichia coli ESBL	4	0.66%
Citrobacter freundii	4	0.66%
Anaerococcus prevotii	4	0.66%
Bacteroides fragilis	4	0.66%
Streptococcus agalactiae MLSB	3	0.49%
Serratia marcescens	3	0.49%
Providencia rettgeri	3	0.49%
Pseudomonas aeruginosa MDR, MBL	3	0.49%
Pseudomonas aeruginosa MDR	3	0.49%
Streptococcus constellatus	2	0.33%
Proteus vulgaris	2	0.33%
Propionibacterium acnes	2	0.33%
Prevotella spp.	2	0.33%
Prevotella melaninogenica	2	0.33%
Peptostreptococcus spp.	2	0.33%
Morganella morganii ESBL	2	0.33%
Enterococcus faecium HLAR, VRE	2	0.33%
Corynebacterium striatum	2	0.33%
Clostridium novyi	2	0.33%
Citrobacter braakii AMP C	2	0.33%
Bacteroides distasonis	2	0.33%
Acinetobacter lwoffii	2	0.33%
Citrobacter braakii	2	0.33%
Streptococcus pyogenes	1	0.16%
Staphylococcus simulans	1	0.16%
Staphylococcus lugdunensis MLSB, MRS	1	0.16%
Staphylococcus epidermidis MRS	1	0.16%
Staphylococcus epidermidis	1	0.16%
Pseudomonas oleovorans	1	0.16%
Proteus mirabilis ESBL	1	0.16%
Prevotella oris	1	0.16%
Prevotella loescheii	1	0.16%
Peptostreptococcus tetradius	1	0.16%
Peptostreptococcus prevotii	1	0.16%
Peptostreptococcus anaerobius	1	0.16%
Pseudomonas aeruginosa MBL	1	0.16%
Lactobacillus paracasei	1	0.16%
Lactobacillus fermentum	1	0.16%
Fusobacterium necrophorum	1	0.16%
Enterococcus faecalis HLAR, VRE	1	0.16%
Enterobacter cloacae AMP C, ESBL	1	0.16%
Enterobacter cloacae AMP C	1	0.16%
Corynebacterium amycolatum	1	0.16%
Clostridium perfringens	1	0.16%
Clostridium subterminale	1	0.16%
Clostridium sporogenes	1	0.16%
Clostridium innocuum	1	0.16%
Clostridium hastiforme	1	0.16%
Citrobacter youngae AMP C	1	0.16%
Citrobacter youngae	1	0.16%
Citrobacter koseri	1	0.16%
Citrobacter freundii ESBL	1	0.16%
Bifidobacterium spp.	1	0.16%
Bacteroides uniformis	1	0.16%
Alcaligenes denitrificans	1	0.16%
Staphylococcus hominis	1	0.16%

Abbreviations: MSS: methicillin-susceptible Staphylococcus; MRSA: methicillin-resistant *Staphylococcus aureus*; MLSB: macrolide-lincosamide-streptogramin B resistance; MDR: multiple drug resistant; ESBL: extended spectrum beta-lactamase; HLAR: high-level aminoglycoside resistance; MBL: metallo-beta-lactamase; VRE: vancomycin-resistant enterococci; AMP C: AmpC beta-lactamases.

index (ABI), Doppler ultrasound of the extremity vessels, computed tomography angiography, angio-MRI, or arteriography [6].

The obtained results were analyzed statistically. In the case of normally distributed variables (identified by the Shapiro-Wilk test) and homogeneity of variance (confirmed

Table 3: Number of particular bacterial isolates in all patients with ischemic diabetic foot syndrome.

	Number of isolates	Percent
Staphylococcus aureus MSS	38	16.10%
Enterococcus faecalis	26	11.02%
Acinetobacter baumannii MDR	14	5.93%
Proteus mirabilis	13	5.51%
Staphylococcus aureus MLSB	13	5.51%
Staphylococcus aureus MRSA, MLSB	11	4.66%
Pseudomonas aeruginosa	10	4.24%
Enterobacter cloacae	9	3.81%
Klebsiella pneumoniae	9	3.81%
Escherichia coli	8	3.39%
Enterococcus faecalis HLAR	7	2.97%
Staphylococcus aureus MRSA	7	2.97%
Streptococcus agalactiae	7	2.97%
Acinetobacter baumannii	6	2.54%
Morganella morganii	4	1.69%
Proteus spp.	4	1.69%
Streptococcus dysgalactiae	4	1.69%
Enterococcus faecium	3	1.27%
Streptococcus mitis	3	1.27%
Streptococcus pyogenes	3	1.27%
Actinomyces naeslundii	2	0.85%
Citrobacter koseri	2	0.85%
Clostridium sporogenes	2	0.85%
Finegoldia magna	2	0.85%
Klebsiella pneumoniae ESBL	2	0.85%
Proteus vulgaris	2	0.85%
Stenotrophomonas maltophilia	2	0.85%
Streptococcus agalactiae MLSB	2	0.85%
Streptococcus constellatus	2	0.85%
Veillonella spp.	2	0.85%
Anaerococcus prevotii	1	0.42%
Bifidobacterium spp.	1	0.42%
Clostridium innocuum	1	0.42%
Enterobacter cloacae AMP C, ESBL	1	0.42%
Enterobacter cloacae ESBL	1	0.42%
Enterococcus faecium HLAR	1	0.42%
Enterococcus faecium HLAR, VRE	1	0.42%
Enterobacter aerogenes	1	0.42%
Gemella morbillorum	1	0.42%
Klebsiella oxytoca	1	0.42%
Klebsiella pneumoniae MBL MDR	1	0.42%
Klebsiella pneumoniae MDR	1	0.42%
Lactobacillus fermentum	1	0.42%
Prevotella spp.	1	0.42%
Providencia stuartii ESBL, AMP C	1	0.42%
Streptococcus dysgalactiae MLSB	1	0.42%
Streptococcus spp.	1	0.42%

Abbreviations: MSS: methicillin-susceptible Staphylococcus; MDR: multiple drug resistant; MLSB: macrolide-lincosamide-streptogramin B resistance; MRSA: methicillin-resistant *Staphylococcus aureus*; HLAR: high-level aminoglycoside resistance; ESBL: extended spectrum beta-lactamase; AMP C: AmpC beta-lactamases; VRE: vancomycin-resistant enterococci; MBL: metallo-beta-lactamase.

by the Levene test), differences between groups were determined using Student's t-test. Alternatively, in the case of nonnormal distributed variables, the Mann–Whitney U test was applied. Intergroup differences in the percentage distributions of dichotomous variables were analyzed with Pearson's χ^2 test. p value < 0.05 was considered statistically significant. All calculations were conducted with the Statistica version 13.3 (TIBCO Software Inc.).

3. Results

The analysis included 844 bacterial strains obtained from 291 patients with DFS (183 males and 108 females) at the mean age of 65.38 (±11.80) years. One bacteria strain was obtained only in 99 people (34.02%), 2 strains in 66 people (22.68%), 3 strains in 44 people (15.12%), and more than 3 strains in 82 cases (28.18%). Gram-positive (no = 426, 50.47%) and Gram-negative strains (no = 418, 49.53%) occurred almost equally often. 52 strains of anaerobic bacteria (6.16%) were isolated.

The most common isolated bacteria were *Staphylococcus aureus* (no = 211, 25.00%), *Enterococcus faecalis* (no = 96, 11.37%), *Enterobacter cloacae* (no = 66, 7.82%), *Pseudomonas aeruginosa* (no = 58, 6.87%), and *Acinetobacter baumannii* (no = 54, 6.40%). All isolated strains are presented in Table 1, in patients with nonischemic DFS in Table 2, and in patients with ischemic DFS in Table 3. As many as 162 isolated strains (19.19%) were found to have at least one resistance mechanism; the most important types of resistance and its percentage shared in particular bacteria are presented in Table 4.

Relationships between the results of laboratory test and the etiological factor were nonsignificant, with the exception of the percentage of glycated hemoglobin A1c (HbA1c). HbA1c was higher in infections with *E. faecalis* than in other bacteria (9.26 vs. 8.68%, $p = 0.02245$); a similar relationship was found for *A. baumannii* (9.31 vs. 8.72%, $p = 0.04768$). On the other hand, in people with *E. cloacae* infection, a lower level of HbA1c was observed compared to other bacteria (8.13 vs. 8.80%, $p = 0.01718$); a similar trend was shown regarding *P. aeruginosa* infection (7.96 vs. 8.81%, $p = 0.00383$).

369 isolates (43.72%) were obtained from people with neuropathic-ischemic DFS, 239 (28.32%) from ischemic DFS, and 236 (27.96%) from neuropathic DFS. In patients with PAD, Gram-negative species were isolated more commonly than in people with normal extremity perfusion (53.18 vs. 40.25%, $p = 0.00077$) (Figure 1), whilst anaerobes were cultured equally often in both groups. In patients with PAD, *E. cloacae* was isolated almost twice as often as in patients with normal extremity perfusion (8.88 vs. 4.66%); in other cases, there were no significant differences in regard to main etiological factors.

Carbapenems, especially meropenem, tigecycline, and aminoglycosides turned out to be the most useful antibiotics in monotherapy followed by 4th and 5th generations of cephalosporins and penicillins with beta-lactamase inhibitors. Their empiric usefulness, however, partially depends on the type of DFS (ischemic or nonischemic). This relationship is

Table 4: Occurrence of particular resistance mechanisms in all analyzed bacterial strains.

Species and resistance mechanism	Percentage of isolated strains with the particular mechanism
Acinetobacter baumannii MDR	70.37%
Staphylococcus aureus MRSA	9.00%
Staphylococcus aureus MLSB	13.74%
Staphylococcus aureus MRSA, MLSB	17.06%
Enterococcus faecalis HLAR	21.88%
Enterococcus faecalis HLAR, VRE (no = 4)	4.17%
Enterococcus faecium HLAR, VRE (no = 3)	17.64%
Enterobacter cloacae ESBL	32.31%
Enterobacter cloacae ESBL, AMP C (no = 2)	3.08%
Klebsiella pneumoniae ESBL	30%
Klebsiella pneumoniae MBL, MDR (no = 1)	0.50%
Escherichia coli ESBL	9.10%
Proteus mirabilis ESBL (no = 1)	3.20%
Morganella morganii ESBL (no = 2)	11.76%
Pseudomonas aeruginosa MDR, MBL (no = 3)	5.17%

MDR: multiple drug resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; MLSB: macrolide-lincosamide-streptogramin B resistance; HLAR: high-level aminoglycoside resistance; VRE: vancomycin-resistant enterococci; ESBL: extended spectrum beta-lactamase; AMP C: AmpC beta-lactamases; MBL: metallo-beta-lactamase.

particularly pronounced in the case of amoxicillin with clavulanate, 1st-generation cephalosporins, and glyco- and lipopeptides (more useful in the neuropathic DFS), as well as ceftazidime, aztreonam, levofloxacin, moxifloxacin, and colistin (more useful in DFS). The differences in the utility of antibacterial agents in particular types of DFS are presented in Table 5. Noteworthily, low sensitivity of bacterial strains to metronidazole, macrolides, and clindamycin was found in all patients.

Patients included in the study were hospitalized, and according to the current guidelines in such circumstance, the empiric treatment should consist of at least two antibacterial agents. The most common treatment regimens cited in the literature and their usefulness in patients with ischemic and nonischemic DFS were analyzed (Table 6). The combination of amoxicillin/clavulanate with vancomycin turned out to be less useful by almost half in people with nonischemic DFS than in patients with coexistent PAD (a similar relationship was also observed for piperacillin/tazobactam and vancomycin); the opposite correlation was found for the combination of carbapenems with vancomycin. Fluoroquinolones together with clindamycin, ceftazidime, and metronidazole showed unacceptably low utility, and the treatment regimen based on ceftazidime with clindamycin was only suitable in 52%.

An attempt was made to establish acceptable and applicable regimens of empiric antibiotic therapy, excluding antibiotics with serious side effects (e.g., colistin and vancomycin), used only in the case of resistance to other drugs and after receiving the results of microbiological culture (e.g., carbapenems) and expensive, hardly available antibiotics (e.g., 4th- and 5th-generation cephalosporins, linezolid, and tigecycline). The results of the analysis are presented in Table 6.

4. Discussion

As in our previous study [7], Gram-positive and Gram-negative strains were isolated with almost the same frequency. It is considered that infections with Gram-positive bacteria are more common in Western communities, whilst Gram-negative bacteria are more common in Eastern communities [8]. However, this explanation seems to be unsatisfactory with respect to the high percentage of Gram-negative bacteria observed in our group. A possible explanation is that the analyzed population included hospitalized patients, previously treated in various hospital wards, with more severe infection involving more than one bacterial strain, commonly with coexistent PAD. Because the Department of Angiology is a part of the general health system, the study group most probably represents the population of hospitalized patients in general.

Despite a similar distribution of Gram-positive and Gram-negative species, the prevalence of particular bacteria is different compared to our study from 2014. The most common isolate in the aforementioned study had been *Enterococcus faecalis* (16.08%), which in the present analysis has taken the second position (11.37%), as nearly one-fourth of all infections are caused by *Staphylococcus aureus* that predominate in the study. *Enterobacter cloacae* was at third place, which may be alarming because of the high tendency of this species to produce mechanisms of antibiotic resistance [9]. *Pseudomonas aeruginosa* continues to be the fourth most frequently isolated pathogen among patients with DFS. The fifth most often isolated pathogen is *Acinetobacter baumannii* (6.40% compared to 2.01% in 2014), which is concerning due to the evidently hospital origin of this strain and its significant resistance to antibiotics [10]. Noteworthily, the low frequency of *Streptococcus* bacteria can partially result from a use of beta-lactam antibiotics as first-line drugs in the general population.

The common occurrence of strains resistant to antibiotics is especially problematic, as many as 20% isolates have at least one resistance mechanism, and the MDR strain accounted for 70% of isolated *Acinetobacter baumannii* (distribution similar to observed in other centers [11]). The resistance of one-fifth of all bacteria in the population with DFS has serious consequences for treatment effectiveness, since standard empiric with antibacterial agents cannot be successful in more than 80% of cases.

In the present analysis, the susceptibility of bacteria to antibiotics was analyzed in relation to algorithms presented in available guidelines [12, 13]. Although monotherapy with meropenem covers 82% of isolated strains, in case of other antibacterial agents, this proportion does not exceed 75% (tigecycline) and 68% (aminoglycosides). Penicillins with beta-lactamase inhibitor were suitable in more than 50% of cases, similar to cephalosporins of 4th generation and 5th generation (with exception of ceftalozane). Some 3rd-generation cephalosporins (ceftriaxone, cefotaxime) were useful in less than 50% of isolates.

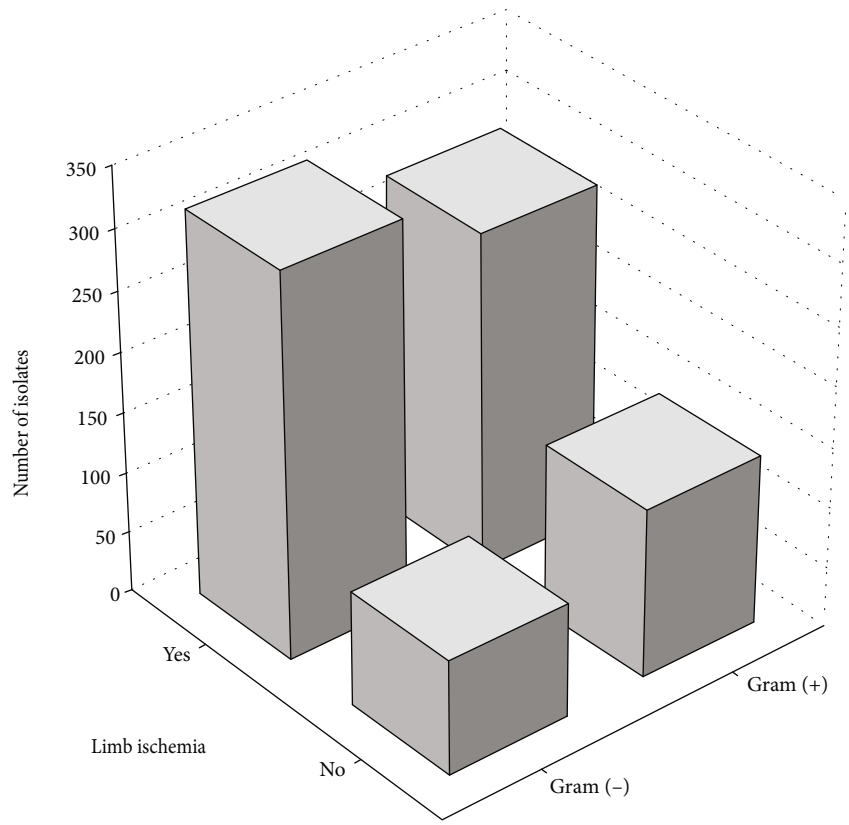

Figure 1: The proportion of Gram-positive and Gram-negative bacteria in patients with and without coexistent peripheral arterial disease (extremity ischemia).

The guidelines in severe infections usually recommend intravenous ciprofloxacin with clindamycin (only 46% accuracy in our study), amoxicillin/clavulanate with vancomycin (62%), piperacillin/tazobactam with vancomycin (87%), amoxicillin/clavulanate with cotrimoxazole (73%), ciprofloxacin with linezolid (64%), and moxifloxacin with linezolid (59%). In the present study, a high proportion of susceptible bacteria have been found in relation to amoxicillin/clavulanate with amikacin (83%) and ceftriaxone with amikacin (77%); more available and cheaper cefuroxime with amikacin has the accuracy of 76%. We also proved low usefulness of some groups of drugs in DFS, i.e., fluoroquinolones and macrolides. Despite the special role of clindamycin and metronidazole in anaerobic infection, their accuracy in this purpose is limited (58% for clindamycin and 54% for metronidazole), compared to amoxicillin/clavulanate (90%).

PAD is an important factor affecting prognosis in patients with DFS. Various analyses have shown different rates of PAD in people with diabetes, ranging from 49% in the EURODIALE study [14] to about 60% in analysis involving smaller populations [15]; however, some researchers postulate that this proportion may be higher [16]. In the analyzed population, the incidence of PAD was 72.02% (including patients with ischemic diabetic foot without neuropathy and mixed, ischemic-neuropathic DFS). In meta-analysis involving over 50,000 patients with DFS, the presence of PAD was associated with two times higher risk of major limb amputation [17]. Nevertheless, data on diversity of particular pathogens and their susceptibility to antibiotics in patients with diabetes and PAS is scarce.

In the present study, it was found that Gram-negative bacteria occurs about 1/4 more frequently in ischemic compared to nonischemic DFS, which may result in a different sensitivity to commonly used groups of antibacterial agents. Moreover, it was shown that bacterial strains isolated from ischemic feet are more resistant to the most commonly used groups of antibiotics, i.e., penicillins (including combinations with their inhibitors), cephalosporins (except for the 4th and 5th generations), glycopeptides, and linezolid. Although the shift towards Gram-negative bacteria is well known in the literature for extremity ischemic ulcers [18], it is uncommonly taken into consideration in the context of DFS.

We can also speculate that differences in isolate patterns between ischemic and nonischemic DFS are not only a consequence of the higher morbidity and more frequent contact with health care but also may result from different local environments of neuropathic and ischemic ulcers. Indeed, in a typical diabetic foot, the infection is driven by neuropathy and its sequelae, hyperglycemia, and probably dysfunction of the immune system [19]. Ischemia may additionally favor the development of Gram-negative bacteria (e.g., there are reports of increased invasiveness of Gram-negative bacteria, e.g., in people with anemia) [20].

There are some limitations in our analysis. Undoubtedly, the effectiveness of a given chemotherapeutic agent is determined by its clinical effect, not by the result of the

Table 5: Susceptibility of bacterial strains to antibiotics in the entire study group, in people with or without PAD (peripheral arterial disease).

Antibacterial agent	Susceptibility in all patients	Susceptibility in patients with PAD	Susceptibility in patients without PAD	Statistical significance, p
Penicillins and penicillins with beta-lactamase inhibitor				
Penicillin G	23%	20%	28%	$p = 0.01891$
Ampicillin	27%	26%	30%	$p = 0.18143$
Amoxicillin	26%	25%	30%	$p = 0.12352$
Amoxicillin with clavulanate	53%	51%	61%	$p = 0.00945$
Piperacillin with tazobactam	57%	57%	59%	$p = 0.58503$
Cephalosporins				
Cephalexin Cephadroxyl Cefazolin Cefaclor	26%	24%	31%	$p = 0.03479$
Cefuroxime	35%	33%	39%	$p = 0.16400$
Ceftazidime	30%	33%	24%	$p = 0.01237$
Cefotaxime	48%	47%	50%	$p = 0.38042$
Ceftriaxone	49%	47%	51%	$p = 0.31700$
Cefixime	31%	32%	27%	$p = 0.17967$
Ceftybuten	30%	32%	27%	$p = 0.19485$
Cefepime	62%	62%	64%	$p = 0.58677$
Ceftalozane	37%	39%	32%	$p = 0.06028$
Ceftaroline	58%	56%	64%	$p = 0.05635$
Monobactams				
Aztreonam	29%	31%	22%	$p = 0.00712$
Carbapenems				
Meropenem	82%	83%	80%	$p = 0.32769$
Imipenem with cilastatin	79%	80%	76%	$p = 0.12597$
Ertapenem	79%	79%	81%	$p = 0.41590$
Glycopeptides				
Vancomycin	50%	46%	58%	$p = 0.00197$
Teicoplanin	50%	46%	59%	$p = 0.00135$
Dalbavancin	50%	47%	59%	$p = 0.00155$
Lipopeptides				
Daptomycin	48%	45%	57%	$p = 0.00199$
Aminoglycosides				
Gentamicin	65%	67%	63%	$p = 0.28476$
Amikacin	65%	66%	65%	$p = 0.86581$
Tobramycin	68%	68%	69%	$p = 0.87520$
Tetracyclines				
Doxycycline	40%	38%	44%	$p = 0.08849$
Glycylcycline				
Tigecycline	75%	53%	80%	$p = 0.05511$
Macrolides				
Erythromycin	9%	9%	11%	$p = 0.34070$
Clarithromycin Azithromycin	9%	8%	10%	$p = 0.46091$
Lincosamides				

Table 5: Continued.

Antibacterial agent	Susceptibility in all patients	Susceptibility in patients with PAD	Susceptibility in patients without PAD	Statistical significance, p
Clindamycin	24%	22%	28%	$p = 0.07191$
Oxazolidinones				
Linezolid	47%	43%	56%	$p = 0.00087$
Fluoroquinolones				
Ciprofloxacin	35%	36%	29%	$p = 0.10831$
Levofloxacin	37%	39%	29%	$p = 0.01410$
Moxifloxacin	31%	34%	24%	$p = 0.02502$
Sulfonamides				
Cotrimoxazole	45%	45%	46%	$p = 0.78042$
Nitroimidazoles				
Metronidazole	4%	5%	2%	$p = 0.02121$
Polymyxins				
Colistin	34%	38%	26%	$p = 0.00155$

Table 6: Susceptibility of isolates to the most commonly recommended combinations of antibacterial agents in the literature in patients with and without peripheral arterial disease (PAD).

Antibacterial agents	Susceptibility in all patients	Susceptibility in patients with PAD	Susceptibility in patients without PAD	Statistical significance, p
Ciprofloxacin with clindamycin	46%	45%	46%	$p = 0.90248$
Levofloxacin with clindamycin	44%	45%	40%	$p = 0.30085$
Amoxicillin/clavulanate with vancomycin	62%	58%	70%	$p = 0.00109$
Piperacillin/tazobactam with vancomycin	87%	85%	94%	$p = 0.00050$
Imipenem with vancomycin	88%	89%	85%	$p = 0.13444$
Meropenem with vancomycin	91%	91%	89%	$p = 0.36788$
Amoxicillin/clavulanate with cotrimoxazole	73%	71%	79%	$p = 0.01562$
Ceftazidime with metronidazole	33%	36%	24%	$p = 0.00178$
Ceftazidime with clindamycin	52%	53%	49%	$p = 0.27473$
Ciprofloxacin with linezolid	64%	61%	69%	$p = 0.07458$
Moxifloxacin with linezolid	59%	58%	63%	$p = 0.28648$

antibiogram, which comprises only one possible variable. Besides drug availability and compliance, the accuracy of therapy is also determined by other factors not included in the analysis, e.g., tissue penetration of antibacterial agents. For example, it is known that vancomycin is characterized by poor tissue penetration, as opposed to aminoglycosides (moderate penetration) or cotrimoxazole (good penetration) [21]; obviously, in DFS therapy, using drugs with good penetration is preferred. Notwithstanding, the result of antibiogram is always the first step in choosing appropriate therapy and reducing the number of modalities to susceptible medications.

5. Conclusions

(1) The most common isolated bacteria in patients with DFS were *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. In patients with PAD and DFS, Gram-negative species were isolated more commonly than in people with neuropathic DFS, whilst anaerobes were cultured equally often in both groups. In patients with PAD, *E. cloacae* was isolated almost twice as often as in patients without PAD

(2) Including all analyzed patients with DFS, monotherapy with meropenem covers 82% of isolated strains, but in the case of other antibacterial agents, this proportion does not exceed 75% (tigecycline) and 68% (aminoglycosides). Penicillins with beta-lactamase inhibitor were useful in more than 50% of cases, similar to cephalosporins of 4th generation and 5th generation (with exception of ceftalozane). Some 3rd-generation cephalosporins (ceftriaxone, cefotaxime) were suitable in less than 50% of isolates. Contrarily, clindamycin, metronidazole, and macrolides are definitely less useful and should not be used in the treatment of DFS

(3) Gram-negative bacteria occur about 1/4 more frequently in ischemic compared to nonischemic DFS, which may result in a different sensitivity to commonly used groups

of antibacterial agents. Moreover, bacterial strains isolated from ischemic feet are more resistant to commonly used antibacterial agents, i.e., penicillins (including penicillins with beta-lactamase inhibitors), cephalosporins (except for the 4^{th} and 5^{th} generations), glycopeptides, and linezolid. In ischemic DFS, merely aztreonam, carbapenems, and fluoroquinolones (a high proportion of resistant strains) appear to be more useful

(4) The most potent combinations of antibacterial agents were carbapenems with vancomycin, piperacillin/tazobactam with vancomycin, ciprofloxacin with linezolid, and moxifloxacin with linezolid. The combinations of fluoroquinolones with clindamycin or ceftazidime with metronidazole showed unacceptably low efficacy. The therapy based on ceftazidime with clindamycin was accurate only in half of the isolates

Data Availability

Data available on request; please contact Rafał Małecki, e-mail: rafal.malecki@umed.wroc.pl.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Correlation between OSAHS and Early Peripheral Atherosclerosis Indices in Patients with Type 2 Diabetes Mellitus in China: A Cross-Sectional Inpatient Study

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Objective: To analyze the differences of early atherosclerosis indices in type 2 diabetes mellitus (T2DM) patients with different degrees of obstructive sleep apnea-hypopnea syndrome (OSAHS) and explore the correlation between them, so as to provide a new clinical basis for the prevention and treatment of early atherosclerosis in patients with T2DM and OSAHS. *Methods*. A prospective study was conducted in 312 patients with T2DM and snoring who were hospitalized in the Department of Endocrinology, Peking University International Hospital from January 2017 to January 2020. According to the monitoring results, 312 patients were divided into 4 groups including the control group (208 cases), mild OSAHS group (18 cases), moderate OSAHS group (38 cases), and severe OSAHS group (48 cases). Multivariate logistic regression analysis was used to analyze the early atherosclerosis indices including brachial-ankle pulse wave velocity (PWV) and ankle-brachial index (ABI) in patients with T2DM coexistence with different degrees of OSAHS. *Results*. (1) As the degree of OSAHS increased, ABI decreased gradually and was lower than that in the control group, but PWV increased and was higher than that in the control group ($p < 0.05$, respectively). (2) The apnea-hypopnea index (AHI) positively correlated with PWV ($r = 0.36$, $p < 0.05$) and negatively correlated with ABI ($r = -0.37$, $p < 0.05$). (3) Multivariate logistic regression showed that after adjusting for age, gender, duration, BMI, blood pressure, blood glucose, blood lipid, and other factors, OSAHS was a risk factor of lower extremity arterial disease (LEAD) in patients with T2DM. With the increase of degree of OSAHS, the risk of lower extremity atherosclerosis gradually increased. *Conclusion*. OSAHS is an independent risk factor of LEAD in patients with T2DM, and with the increase of AHI, the ABI and PWV have changed, which provides a new clinical basis for the prevention and the treatment of early atherosclerosis in patients with T2DM and OSAHS.

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) in China is increasing year by year. The main reasons of death in patients with T2DM are complications such as lower extremity arterial disease (LEAD) [1]. Obstructive sleep apnea-hypopnea syndrome (OSAHS), as a common disease of sleep disordered breathing, has gradually attracted attention in recent years. OSAHS and T2DM often coexist. The incidence rate of OSAHS in T2DM patients is 18-36%, while in OSAHS patients, the incidence rate of T2DM is about 40% [2].

Atherosclerosis is a systemic disease involving the thickening and hardening of the arterial walls. Patients with T2DM are more likely to develop atherosclerotic diseases, and nearly 75% of deaths in patients with T2DM is directly due to atherosclerotic diseases, with coronary heart disease posing the highest mortality [3].In recent years, it has been reported that the prevalence of diabetic macrovascular and microvascular complications in T2DM patients with OSAHS is significantly increased [4, 5]. However, a limited number of studies have reported on whether there is a correlation between the early peripheral atherosclerosis indices and

OSAHS in patients with T2DM. The indices including the ankle-brachial index (ABI) and brachial-ankle pulse wave velocity (PWV) are noninvasive indicators for assessing the early changes of atherosclerosis.

The purpose of this study is to analyze the differences and changes of early atherosclerosis indices in T2DM patients with different degrees of OSAHS and aimed at providing a new clinical basis for the prevention and treatment of atherosclerosis in these patients.

2. Materials and Methods

2.1. Patients and Study Design. This is a prospective study. 312 patients including 208 males and 104 females with T2DM and snoring who were hospitalized in the Department of Endocrinology, Peking University International Hospital from January 2017 to January 2020 were enrolled in this study. The T2DM diagnostic criteria were based on the 1999 World Health Organization's diagnostic criteria [6], including (1) random blood glucose levels ≥ 11.1 mmol/l, (2) fasting blood glucose levels ≥ 7.0 mmol/l, and (3) OGTT test with blood glucose levels ≥ 11.1 mmol/l at 2 hours after receiving 75 g of glucose. In the absence of diabetic symptoms, the OGTT test was repeated on the patient the next day to confirm. If one or more of the three criteria were met, the patient was diagnosed with DM. In addition, according to the clinical classification, the patient was diagnosed with T2DM. The exclusion criteria for this study included a history of end-stage renal disease, cancer, stroke, cardiovascular disease, or hormone-related endocrine disease, lower extremity vascular occlusions, or arterial calcification disease. This study was approved by Bioethics Committee of Peking University International Hospital. All participants have signed the informed consent form.

2.2. Polysomnography (PSG) Examination. None of the subjects had been diagnosed with OSAHS, and all the patients carried out the all-night PSG monitoring in the sleep monitoring center of Peking University International Hospital. The monitoring indices included the electroencephalogram (EEG) which was obtained with C4A1, C3A2, 01A2, and 02A1 leads; electrooculogram (EOG); mandibular mental electromyography (EMG); electrocardiogram (ECG); respiratory airflow; thoracoabdominal respiratory movement; blood oxygen saturation (SaO_2); body position; snoring; and EMG of tibial anterior muscle. Sleep monitoring time was not less than 7 hours at night. Patients were asked not to use sedatives, coffee, wine, or strong tea on the day of sleep monitoring. The apnea-hypopnea index (AHI) means the sum of the average number of apnea and hypopnea per hour.

According to the Chinese diagnostic criteria of OSHAS [7], Apnea and hypopnea recurred more than 30 times or AHI ≥ 5/h during 7 hour-sleep. Apnea events were mainly obstructive, accompanied by snoring, sleep apnea, daytime sleepiness, and other symptoms.

According to AHI, patients were divided into four groups: the control group, mild group (AHI was 5-15/h), moderate group (AHI was 16-30/h), and severe group (AHI > 30/h).

2.3. Medical Records and Clinical Data. Medical history and relevant clinical indices were recorded, including age, gender, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and diabetes duration. From the medical records, the body mass index (BMI) was calculated by the formula weight/height^2 (kg/m^2).

2.4. Laboratory Tests. The patients were required to fast for 8 hours prior to blood collection. The blood tests included fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), serum creatinine (sCr), uric acid (UA), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Postprandial blood glucose (PBG) was collected 2 h after a mixed nutrient load. All blood tests were performed at Peking University International Hospital. FBG, PBG, sCr, UA, TC, TG, LDL-C, and HDL-C were measured by using enzyme-linked immunosorbent assay methods, while HbA1c was measured by high-performance liquid chromatography (HPLC). Glomerular filtration rates (eGFR) were calculated using the sCr levels according to the CKD-EPI-ASIA equation as follows:

For males,

$$\begin{aligned} sCr \le 0.9 mg/dl &: eGFR_{CKD-EPI-ASIA} = 141 \times (sCr/0.9) - 0.411 \times 0.993^{age} \times 1.057, \\ sCr > 0.9 mg/dl &: eGFR_{CKD-EPI-ASIA} = 141 \times (sCr/0.9) - 1.209 \times 0.993^{age} \times 1.057. \end{aligned} \quad (1)$$

For females,

$$\begin{aligned} sCr \le 0.7 mg/dl &: eGFR_{CKD-EPI-ASIA} = 141 \times (sCr/0.7) - 0.329 \times 0.993^{age} \times 1.049, \\ sCr > 0.7 mg/dl &: eGFR_{CKD-EPI-ASIA} = 141 \times (sCr/0.7) - 1.209 \times 0.993^{age} \times 1.049. \end{aligned} \quad (2)$$

2.5. Early Atherosclerotic Indices. ABI (ankle-brachial index) and PWV (brachial-ankle pulse wave velocity) measurements were used to assess the degree of atherosclerosis. The BP-203 III automatic atherosclerosis analyzer (Omron, Tokyo, Japan) was used to measure the ABI and PWV values. Patients were allowed to rest for 5 min before measuring the systolic pressure of the right and left anterior tibial artery (ankle) and the right and left brachial artery (brachial artery). The left and right ABI were calculated as the systolic ankle pressure divided by the systolic brachial pressure. PWV was calculated as the time interval between the anterior tibial artery (ankle) and the initial segment of the pressure wave for the brachial artery and the distance between the two selected components. ABI and PWV values were measured and assessed by the same group of physicians in the Department of Endocrinology to avoid potential interexaminer differences. The ABI and PWV averages were calculated by determining the mean value between the left and right ABI and PWV.

2.6. Doppler Ultrasonography for Measuring LEAD. The arteries of both lower extremities were examined by ultrasound professional technician using lower extremity arterial color Doppler ultrasonography (Phillips iE33, Washington, DC, USA). The patients were in supine position, and bilateral

lower extremity arteries (total femoral, femoral deep, superficial, popliteal, anterior tibial, posterior tibial, dorsum of foot) were examined. The examination contents included artery diameter and intimamedia thickness of lower extremity artery, whether there was plaques and whether there was vascular stenosis. The coefficient of variance was 1.92%. According to the ultrasound results, if the patient has lower extremity artery stenosis or occlusion, the patient is diagnosed as LEAD.

2.7. Statistical Analysis. Statistical analysis was performed with the SPSS Version 21.0 software (IBM, Chicago, IL, USA). The data were analyzed using the Kolmogorov-Smirnov test, and all variables had a normal distribution and were expressed as the mean ± standard deviation. Multigroup comparisons of the sample were compared with the one-way analysis of variance (ANOVA). The least significant difference (LSD) method was used to compare the statistical significance between the groups. Count data were compared as ratios statistically, and the χ^2 test was used for comparison among the four groups. Pearson correlation analysis and multivariate linear regression were used to assess the association between ABI, PWV, and AHI. Multivariate logistic regression was used to assess the factor of LEAD in T2DM patients with OSAHS. p values <0.05 were considered statistically significant.

3. Results

3.1. Comparison of General Characteristics, Biochemical Indices, PSG Indices, and Atherosclerotic Indices among the Four Groups. Compared with the control group, the patients with OSAHS were older and had higher BMI. There were significant differences among the four groups ($p < 0.05$, respectively). Among the four groups, SBP of patients with OSAHS was significantly higher than that of the control group, and the UA level was significantly higher than that of the control group ($p < 0.05$, respectively). At the same time, the results showed that ABI in the OSAHS group was lower than that in the control group, while PWV was higher in the OSAHS group than that in the control group ($p < 0.05$, respectively). The proportion of OSAHS coexisted with LEAD was higher, and as the severity increasing of OSAHS, the proportion with LEAD increased gradually ($p < 0.05$). There was no significant difference in the gender ratio, diabetic duration, blood lipid, blood glucose, UACR, and eGFR among the four groups ($p > 0.05$, respectively) (shown as Table 1).

3.2. Correlation Analysis between AHI Level and General Characteristics, Biochemical Indices, ABI, and PWV. Age, BMI, TC, TG, LDL-C, ABI, and PWV levels were positively significantly correlated with AHI ($p < 0.05$, respectively). ABI was negatively correlated with AHI ($r = -0.37$, $p < 0.05$), while PWV positively correlated with AHI ($r = 0.36$, $p < 0.05$) (shown as Table 2).

3.3. Multiple Stepwise Linear Regression Results among AHI, ABI, and PWV. With ABI and PWV as dependent variables, respectively, AHI, age, gender, BMI, diabetic duration, blood glucose, blood pressure, blood lipid, UA and other indices as independent variables, and multiple linear regression model were established. The results showed that after adjusting for age, gender, BMI, diabetic duration, blood glucose, blood pressure, blood lipid, and UA, AHI was an independent risk factor for decreased ABI and increased PWV (shown as Table 3).

3.4. Multivariate Logistic Regression Results of LEAD in T2DM Patients with OSAHS. With LEAD as a dependent variable, the results showed that AHI was an independent risk factor for LEAD in patients with T2DM.After adjusting for age, gender, BMI, diabetic duration, blood glucose, blood pressure, blood lipid, UA, and other indices, AHI was still an independent risk factor for LEAD in patients with T2DM. With the increasing degree of OSAHS, the risk of LEAD in patients increased gradually (shown as Table 4).

Model 2 is adjusted for age, gender, diabetic duration, BMI, blood glucose, blood pressure, blood lipid, and UA. Abbreviations: ABI: ankle-brachial index; PWV: brachial-ankle pulse wave velocity; AHI: apnea-hypopnea index.

4. Discussion

As the main type of diabetes, T2DM has a high morbidity and mortality rate, which brings a certain economic burden to the society and family. OSAHS is a disease characterized by recurrent upper airway stenosis or obstruction during sleep. Complete closure of the upper airway leads to obstructive sleep apnea, and incomplete closure leads to hypopnea. The prevalence of OSAHS in patients with T2DM was significantly higher than that in the general population, and the prevalence of OSAHS in hospitalized T2DM patients was as high as 60% [8]. Patients with coexistence of the two diseases have a significantly higher risk of stroke and cardiovascular disease [9].

Studies have shown that the risk of macrovascular complications in patients with OSAHS and T2DM is significantly increased [10], and the related pathophysiological mechanisms are multifaceted. Intermittent hypoxia and insulin resistance in OSAHS patients can promote the increase of inflammatory markers, including nitric oxide (NO), endothelin-1(ET-1), interleukin-6 (IL-6), and C-reactive protein (CRP). These inflammatory factors affect the vascular endothelial function and participate in inflammatory vascular remodeling and atherosclerosis formation and development. At the same time, studies have found that there are oxidative stress reactions leading to tissue ischemia and hypoxia in patients with OSAHS, including reactive oxygen species (ROS), vascular endothelial growth factor (VEGF), advanced glycation end products (AGEs), and plasminogen activator inhibitor-1 (PAI-1), which leads to the occurrence and development of diabetic vascular disease [11, 12]. Excessive ROS can inhibit insulin-induced energy uptake in fat and muscle tissues, damage islet beta cells, inhibit insulin secretion, and aggravate insulin resistance. Studies have shown that there is upregulated oxidative stress in OSAHS patients, which may have adverse effects on cardiovascular diseases [13]. ET-1 is a vasoconstrictor and can induce inflammatory vascular remodeling, which may be

Table 1: Comparison of general characteristics, biochemical indices, PSG indices, and atherosclerosis indices among the four groups.

Index	Control group ($n = 208$)	Mild group ($n = 18$)	Moderate group ($n = 38$)	Severe group ($n = 48$)	F (X^2)	p
Age(y)	47.80 ± 13.61	55.78 ± 9.43[a]	54.32 ± 12.57[a]	52.33 ± 12.86[a]	4.91	<0.05
Gender (male%)	130 (62.5%)	12 (66.67%)	30 (78.95%)	36 (75%)	2.85	0.42
BMI (kg/m^2)	26.16 ± 3.71	27.20 ± 3.52[a]	27.90 ± 4.97[a]	30.15 ± 4.05[a,b,c]	13.80	<0.05
Diabetic duration (y)	6.51 ± 7.10	8.78 ± 6.59	9.33 ± 7.68	7.78 ± 6.94	2.32	0.19
AHI	2.65 ± 0.78	9.44 ± 2.77[a]	23.26 ± 4.15[a,b]	49.12 ± 13.49[a,b,c]	72.45	<0.05
Minimum SaO_2 (%)	97.32 ± 5.64	87.76 ± 2.12[a]	81.34 ± 3.47[a,b]	68.85 ± 2.66[a,b,c]	7.86	<0.05
SBP (mmHg)	130.58 ± 16.10	140.00 ± 13.12[a]	140.63 ± 12.05[a]	140.83 ± 11.72[a]	10.49	<0.05
DBP (mmHg)	79.39 ± 11.41	81.00 ± 10.00	79.84 ± 10.96	82.79 ± 11.09	1.24	0.30
FBG (mmol/l)	9.18 ± 3.56	8.11 ± 2.79	8.60 ± 3.07	9.43 ± 3.78	0.41	0.74
PBG (mmol/l)	13.20 ± 5.67	14.15 ± 5.34	14.19 ± 6.94	13.08 ± 3.62	0.44	0.72
HbA1c (%)	8.54 ± 1.96	8.11 ± 1.62	8.38 ± 1.61	8.31 ± 1.79	0.43	0.73
TC (mmol/l)	4.53 ± 1.14	4.48 ± 0.95	4.14 ± 0.93	4.62 ± 1.47	1.41	0.24
TG (mmol/l)	2.52 ± 1.83	2.03 ± 1.13	1.82 ± 0.74	2.52 ± 1.83	2.13	0.10
LDL-C (mmol/l)	2.65 ± 0.87	2.74 ± 0.76	2.32 ± 0.79	2.80 ± 1.23	2.06	0.11
HDL-C (mmol/l)	0.96 ± 0.24	0.91 ± 0.28	0.91 ± 0.26	0.94 ± 0.16	0.47	0.70
UA (umol/l)	346.52 ± 89.89	359.22 ± 91.36	397.11 ± 79.48[a,b]	381.14 ± 77.22[a]	4.79	<0.05
eGFR (ml/min/1.73m^2)	102.49 ± 18.04	96.26 ± 16.86	95.16 ± 14.41	98.64 ± 17.14	2.55	0.06
UACR (mg/g)	21.57 ± 39.81	37.97 ± 41.95	32.65 ± 42.08	31.94 ± 59.40	1.70	0.17
ABI	1.15 ± 0.09	1.14 ± 0.06[a]	1.14 ± 0.09[a]	1.05 ± 0.15[a,b,c]	12.34	<0.05
PWV (cm/s)	1435.05 ± 289.29	1487.73 ± 283.90[a]	1720.08 ± 281.15[a]	1801.89 ± 498.59[a,b,c]	17.62	<0.05
LEAD (%)	18 (8.65%)	8 (44.44%)[a]	18 (47.36%)[a]	34 (70.83%)[a,b,c]	61.75	<0.05

[a]$p < 0.05$ compared with the control group, [b]$p < 0.05$ compared with the mild group, [c]$p < 0.05$ compared with the moderate group. Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; FBG: fasting blood glucose; PBG: postprandial blood glucose; HbA1c: glycosylated hemoglobin; UA: uric acid; TC: total cholesterol, TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ABI: ankle-brachial index; PWV: brachial-ankle pulse wave velocity; AHI: apnea-hypopnea index; LEAD: lower extremity arterial disease.

Table 2: Linear correlation analysis between AHI and general characteristics, biochemical indices, ABI, and PWV.

	AHI			AHI	
Index	R	p	Index	R	p
Age (y)	0.02	<0.05	TC (mmol/l)	0.30	<0.05
Diabetic duration (y)	-0.18	0.06	TG (mmol/l)	0.28	<0.05
BMI (kg/m^2)	0.32	<0.05	LDL-C (mmol/l)	0.34	<0.05
SBP (mmHg)	0.11	0.27	HDL-C (mmol/l)	0.03	0.74
DBP (mmHg)	0.14	0.16	eGFR (ml/min/1.73m^2)	0.05	0.64
FBG (mmol/l)	0.11	0.30	UACR (mg/g)	0.10	0.32
PBG (mmol/l)	0.13	0.23	UA (umol/l)	0.17	0.10
HbA1c (%)	0.04	0.73	ABI	-0.37	<0.05
			PWV (cm/s)	0.36	<0.05

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; FBG: fasting blood glucose; PBG: postprandial blood glucose; HbA1c: glycosylated hemoglobin; UA: uric acid; TC: total cholesterol, TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; AHI: apnea-hypopnea index; ABI: ankle-brachial index; PWV: brachial-ankle pulse wave velocity.

associated with increased cardiovascular risk in patients with OSAHS [14]. VEGF is a hypoxia sensitive glycoprotein. In severe hypoxic patients with OSAHS, the plasma level of VEGF is increased. VEGF stimulates angiogenesis by promoting the proliferation, migration, and proteolysis of vascular endothelial cells [15]. Relevant studies have proved that the level of AGEs in patients with T2DM is increased [16]. The AGE pathway is the main pathophysiological mechanism of diabetic vascular disease development. The accumulation of AGEs in OSAHS may lead to the decrease of

Table 3: Multiple stepwise linear regression results between AHI level with ABI and PWV.

Index	ABI			PWV		
	βst	t	p	βst	t	p
Model 1						
AHI	0.01	5.34	$p < 0.05$	26.26	6.46	$p < 0.05$
Model 2						
AHI	0.01	5.15	$p < 0.05$	27.24	6.16	$p < 0.05$
Model 3						
AHI	0.01	5.19	$p < 0.05$	26.92	5.68	$p < 0.05$

Model 2 is adjusted for age, gender, and BMI; model 3 is adjusted for age, gender, diabetic duration, BMI, blood glucose, blood pressure, blood lipid, and UA. Abbreviations: ABI: ankle-brachial index; PWV: brachial-ankle pulse wave velocity; AHI: apnea-hypopnea index.

Table 4: Multivariate logistic regression results of OSAHS and LEAD in patients with T2DM.

Index	OR	LEAD 95% CI	p
Model 1			
Control group	1	1	
Mild group	8.44	2.96, 24.08	$p < 0.05$
Moderate group	25.63	11.66, 56.37	$p < 0.05$
Severe group	29.56	12.40, 70.47	$p < 0.05$
Model 2			
Control group	1	1	
Mild group	6.83	2.28, 20.46	$p < 0.05$
Moderate group	27.00	11.56, 63.08	$p < 0.05$
Severe group	28.07	11.08, 71.12	$p < 0.05$

endothelial progenitor cells and endothelial repair ability over time, which may lead to the onset of cardiovascular disease.

Several studies have shown the effects of OSA on diabetic macrovascular complications. A longitudinal study in 132 T2DM patients, followed for 4.9 years, revealed that sleep-disordered breathing was a predictor of incident coronary artery disease with a hazard ratio of 1.9 (95% CI: 1.1, 3.3), as well as an increased risk of heart failure [17]. In the Sleep AHEAD study which included 305 T2DM patients, AHI was associated with a 2.57-fold increase in risk of having a history of stroke [18]. A study of 131 patients with T2DM has shown that patients with moderate-to-severe OSAHS and hypertension were three times more likely to have diabetes-related complications compared to those with no or mild OSAHS [19]. In our study, we focused on LEAD as the diabetic macrovascular complications. The results showed that, after adjusting for age, diabetic duration, blood glucose, blood lipid, and other factors, OSAHS was still an independent risk factor of LEAD in patients with T2DM. Also, we further analyzed the influence of different degrees of OSAHS on the occurrence of LEAD in patients. The results showed that mild OSAHS was a predictor of LEAD with a OR of 6.83 (95% CI: 2.28, 20.46) moderate OSAHS with a OR of 27.00 (95% CI: 11.56, 63.08), and severe OSAHS with a OR of 28.07(95% CI: 11.08, 71.12). It was found that with the increasing severity of OSAHS, the risk of LEAD in patients with T2DM was increasing.

Many studies have shown the closely significant relationship between OSAHS and atherosclerosis disease [20, 21]. There are also some studies focused on the association between PWV and AHI [22–24], but the conclusion is inconsistent. A recent study found that in obese patients, AHI was an independent predictor for higher PWV ($r = 0.352$, $p = 0.038$) [22]. Another study also found that the normal-weight sleep breath disorder group had higher PWV than the control group ($p = 0.03$) [23], but a meta-analysis showed that elevated arterial stiffness in patients with OSA is driven by conventional cardiovascular risk factors rather than apnea parameters [24]. However, there are few reports on whether OSAHS affects the early arterial structure and function of patients with T2DM. Clinically, ABI and PWV can reflect the early changes of the arterial structure and function in patients with T2DM. This study found that in T2DM patients with OSAHS, the ABI was significantly lower than that in the control group, and the PWV was significantly increased. At the same time, after adjusting for age, gender, BMI, diabetic duration, blood glucose, blood pressure, blood lipids, and other factors, AHI was still an independent risk factor of increased ABI and decreased PWV. This suggests that the changes of the peripheral arterial structure and function may occur earlier in T2DM patients with OSAHS, and AHI is an independent risk factor of early changes of peripheral arterial disease.

There are some limitations in this study. First of all, the subjects are all hospitalized patients, and the average age of patients in our study is too old to represent all T2DM patients, especially not represent the newly diagnosed T2DM patients. Secondly, the sample size needs to be further expanded. Thirdly, it is only a cross-sectional study of inpatient data, without outpatient data, and lack of longitudinal follow-up data of patients.

5. Conclusion

OSAHS is an independent risk factor of atherosclerosis in patients with T2DM, and with the increased severity of OSAHS, the risk of LEAD gradually increases. At the same time, T2DM patients with OSAHS may have early changes of the arterial function, which provides a new clinical basis for the early diagnosis and prevention of LEAD in T2DM patients with OSAHS.

Data Availability

The data used to support the findings of this study are available from the corresponding author and first author upon request.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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