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Professional paper

METABOLIC PROFILE AND PERIPHERAL ARTERIAL DISEASE-ASSOCIATED SYMPTOMS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A CROSS-SECTIONAL STUDY

Stojka DOKUZOVA[1], Nevenka VELICKOVA[1], Martina Gjorgjievska KAMCEVA[1]

[1]Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia
Corresponding author:
Stojka Dokuzova
Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia
E-mail: stojka.311144@student.ugd.edu.mk

Abstract

Introduction: Peripheral arterial disease (PAD) is one of the most common macrovascular complications in patients with type 2 diabetes mellitus (T2DM). Previous international studies such as the UKPDS, ADVANCE, and ACCORD trials demonstrated a strong association between poor glycaemic control, cardiovascular risk and progression of vascular complications in patients with diabetes mellitus. Peripheral arterial disease is an important marker for generalized atherosclerosis. Doppler ultrasonography is non-invasive method for localization and assessment of the degree of stenosis or occlusion in the arteries that supply blood to the extremities.
Materials and Methods: This cross-sectional observational study included a total of 230 patients with peripheral arterial disease, 200 with and 30 patients without T2DM treated at the Department of Internal Diseases, Clinical Hospital Stip. The research design of this study is descriptive and correlational and the obtained data are processed using the Python programming language for statistical analysis and data processing. Diabetes duration, smoking status, body mass index (BMI), fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels were analysed. The arithmetic mean, standard deviation, median, interquartile range, minimum and maximum value were calculated for each laboratory parameter. Doppler ultrasonography was performed at every patient with symptoms associated with PAD.
Results: The prevalence of peripheral arterial disease is higher in patients with diabetes and obesity, the duration of diabetes is significant from the aspect of cumulative effect, smoking is an important modifying risk factor, impaired lipid profile, especially increased triglycerides are closely related to increased fasting glycemia and increased HBA1C in patients with peripheral arterial disease and T2DM.
Conclusion: Poor metabolic control is associated with increased PAD-related symptoms in patients with T2DM. Early identification of vascular symptoms, doppler ultrasonography for screening and optimization of glycaemic and lipid parameters may improve vascular outcomes.

Keywords: *diabetes mellitus, peripheral arterial disease, HbA1c, Doppler ultrasonography*

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia caused by insulin resistance and/or impaired insulin secretion. The global prevalence of T2DM has significantly increased during recent decades. The International Diabetes Federation-IDF estimated that the number of people worldwide suffer from diabetes is expected to increase to 592 million by 2035. Long duration of diabetes is strongly associated with the development of microvascular and macrovascular complications that lead to morbidity, disability and mortality [1, 2]. Peripheral arterial disease (PAD) is one of the most important macrovascular manifestations of T2DM associated with impaired mobility, reduced quality of life, increased hospitalization and cardiovascular mortality. PAD is characterized by progressive atherosclerotic narrowing of peripheral arteries in the lower extremities and

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ischemic symptoms. In diabetic patients, PAD often develops earlier and progresses more aggressively. Chronic hyperglycaemia, dyslipidaemia, endothelial dysfunction and oxidative stress are very important for progression of these disease. Dyslipidaemia characterized by elevated low-density lipoprotein (LDL) cholesterol and triglycerides together with reduced high-density lipoprotein (HDL) cholesterol increases vascular risk in diabetic patients. Hyperglycaemia led to endothelial dysfunction, vascular inflammation and atherosclerosis in different metabolic pathways. These pathophysiological mechanisms increase arterial stiffness and impair vascular circulation, thereby predisposing patients to symptomatic PAD [1-3]. Patients with T2DM develop symptoms associated with PAD including intermittent claudication, lower extremity pain, numbness, cold extremities and impaired walking distance. Early recognition of PAD-associated symptoms is clinically important because delayed diagnosis may result in advanced vascular disease, tissue ischemia, ulceration, infection and lower extremity amputation. PAD is strongly associated with increased risk of myocardial infarction, stroke and cardiovascular death. Screening and early identification of high-risk diabetic patients should become of essential meaning in routine clinical practice [4]. Our study aimed to evaluate the relationship between glycaemic control, lipid profile, symptoms associated with peripheral arterial disease and the degree of vascular changes noted with Doppler ultrasonography in patients with type 2 diabetes mellitus. Metabolic optimization and regular vascular assessment in diabetic patients with prolonged disease duration and unfavourable metabolic parameters is crucial for better outcome.

Materials and Methods

Study Design

A cross-sectional observational study was conducted at the Department of Internal Diseases, Clinical Hospital Stip, North Macedonia.

The study included a total of 230 adult patients diagnosed with symptoms suggestive of peripheral arterial disease, of which 200 have T2DM and 30 patients without T2DM. Doppler ultrasonography was performed at every patient. The study population was divided into two groups:

- Group 1: 200 patients with peripheral arterial disease and type 2 diabetes mellitus
- Group 2: 30 patients with peripheral arterial disease without diabetes mellitus.

All paricipants were adults and were evaluated according to a standardized clinical protocol. These parameters were analyzed: presence of T2DM, duration of diabetes, smoking status, body mass index (BMI), fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and the degree of vascular changes and symptoms associated with PAD noticed with Doppler ultrasonography.

Inclusion criteria include: patients aged over 18 years, presence of symptoms suggestive of peripheral arterial disease and signed informed consent. Exclusion Criteria include patients with type 1 diabetes mellitus, pregnancy and active malignancy.

Clinical and Laboratory Assessment

All participants underwent clinical examination and laboratory evaluation. Blood samples were collected after overnight fasting. The following parameters were analysed: fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Body mass index (BMI) was calculated according to the following formula: BMI (kg/m^2)=body weight (kg)/ $height^2$ (m^2).

Participants were classified according to BMI using the following categories:
-Underweight: BMI<18,5 kg/m^2
-Normal weight: BMI 18,5-24,9 kg/m^2
-Overweight: BMI 25,0-29,9 kg/m^2
-Obesity: BMI>30.0 kg/m^2;
Smoking status and the degree of vascular changes noted with Doppler ultrasonography were also evaluated.

Ethical Considerations

Written informed consent was obtained from all participants after explanation of the study protocol and study objectives. Ethical approval for the study was obtained from the Ethical Committee of Clinical Hospital Stip and Ethical committee of Faculty of medical sciences in Stip.

Statistical Analysis

For statistical analysis, continuous variables were expressed as mean ± standard deviation (SD), or median and interquartile range, as appropriate based on data distribution. Categorical variables were presented as absolute numbers and percentages. Comparative analyses between groups were performed using Student's t-test or Mann–Whitney U test depending on data distribution. Correlation analyses were performed using Pearson or Spearman correlation coefficients. Statistical significance was defined as $p<0.05$.

Results

A total of 230 patients with peripheral arterial disease were included in the study. Of these 200 (87.0%) had type 2 diabetes mellitus, whereas 30 (13.0%) did not have diabetes mellitus.

Table 1. Distribution of participants according to the presence of type 2 Diabetes Mellitus

Variable	N	%
With T2DM	200	87
Without T2DM	30	13

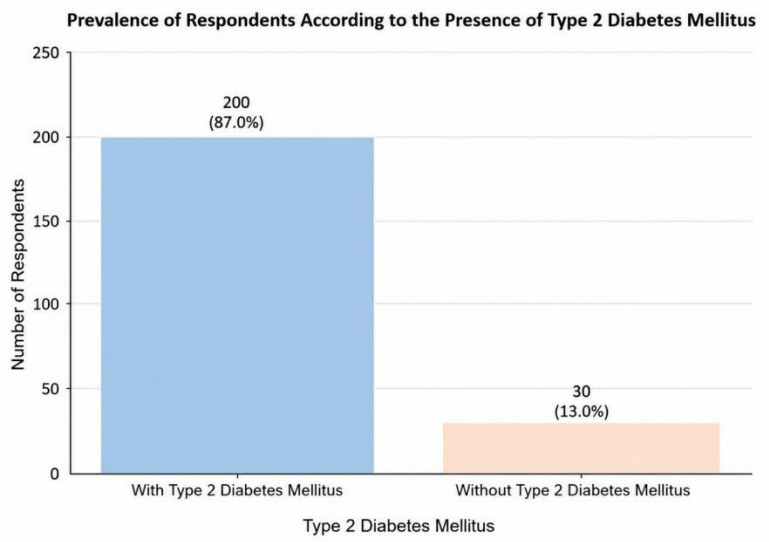


Figure 1. Distribution of participants according to the presence of type 2 diabetes mellitus

This study demonstrated a significant association between poor glycaemic regulation, unfavorable lipid profile at patients with type 2 diabetes mellitus and PAD. Patients with higher HbA1c values showed more metabolic abnormalities compared with patients with better glycaemic control. These findings support the concept that chronic hyperglycaemia and dyslipidaemias are major factors that lead to diabetic macrovascular complications. One of the most important findings in this study was the association between longer duration of diabetes and increased PAD-related symptoms. Patients with poorer glycaemic control had significantly longer duration of diabetes. This finding is clinically very important because prolonged exposure to hyperglycaemia progressively damages the vascular endothelium and accelerates atherosclerotic changes in peripheral arteries. The elevated fasting plasma glucose levels in patients with HbA1c > 6,5 % indicate poor glycoregulation and hyperglycaemia. HbA1c reflects average blood glucose levels over three months and is considered one of the most important biomarkers for glycaemic control. Elevated HbA1c values have been associated with increased cardiovascular risk and vascular complications in many studies. In our study patients with elevated HbA1c values demonstrated increased prevalence of intermittent claudication, lower limb pain, numbness, cold extremities and reduced walking distance. These findings indicate that poor glycaemic regulation may be the reason directly to symptomatic vascular insufficiency. The lipid profile analysis demonstrated significantly higher triglyceride values in patients with poorer glycaemic control. In diabetic patients' dyslipidaemia is one of the most important risk factors for atherosclerosis and vascular diseases. Hyperglycaemia and dyslipidaemia accelerate atherosclerotic plaque formation in peripheral arteries. Intermittent claudication is one of the most characteristic clinical manifestations of PAD. Patients with T2DM present with atypical symptoms because concomitant diabetic neuropathy may mask ischemic pain. PAD often remains underdiagnosed until advanced stages of disease.

Smoking is one of the strongest modifiable risk factors for PAD because it accelerates endothelial injury, promotes thrombosis, and worsens arterial inflammation. This combined exposure to smoking and chronic hyperglycaemia may produce synergistic vascular damage and increase cardiovascular risk.

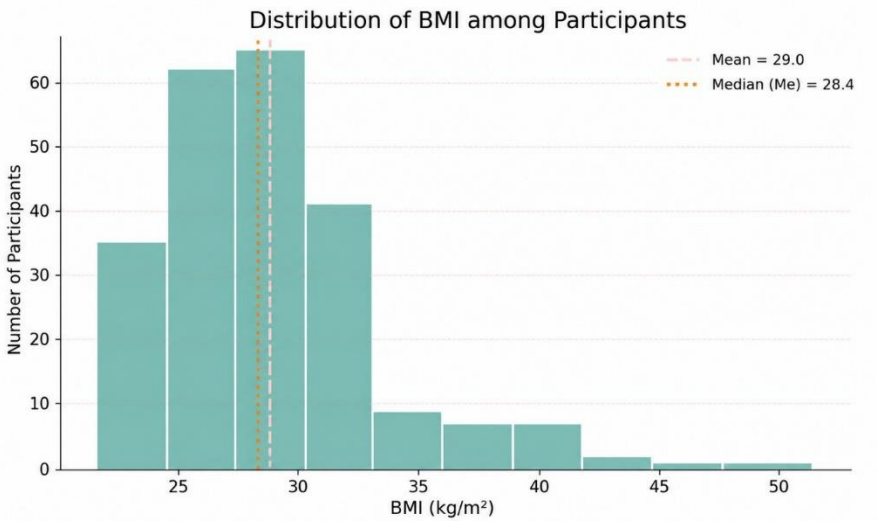


Figure 2. Distribution of participants by BMI

The average value of the body mass index is 28,96 kg/m2 with a standard deviation of 4,54 kg/m2. The median BMI is 28,45kg/m2 and the interquartile range is 26 to 31,2 kg/m2. The minimum value of BMI is 21,7 kg/m2, while the maximum value is 50,8 kg/m2.

Table 2. Distribution of Participants by Body Mass Index (BMI) Category

BMI category	N	%
BMI<25 kg/m2	43	18.7
BMI25-30kg/m2	108	47
BMI>30kg/m2	79	34.3

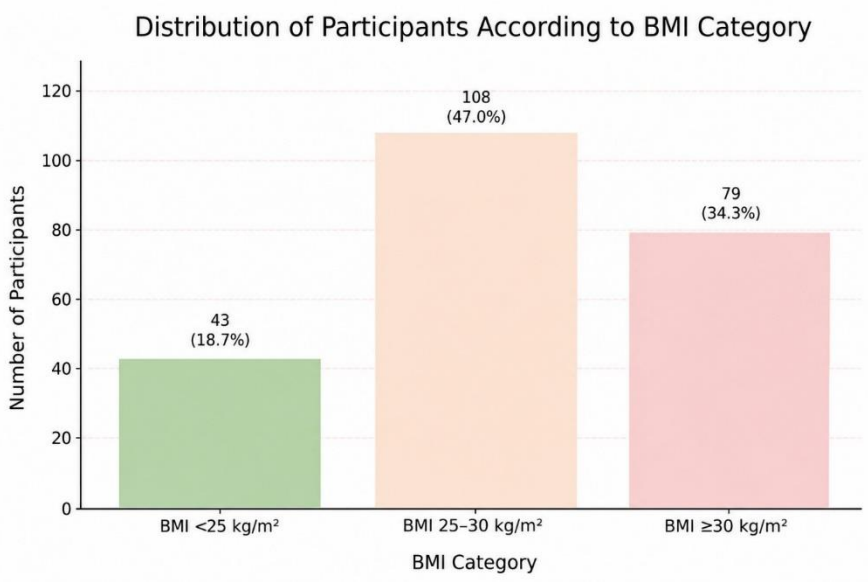


Figure 3. Distribution of participants by BMI category

According to the BMI categories, the largest part of the patients is in the overweight category with a BMI of 25-30 kg/m2, 108 patients, which represents 47,0% of the sample. Normal body weight <25 kg/m2 have 43 patients or 18,7%, while 79 patients or 34,3% have BMI >30 kg/m2

which corresponds to the category of obesity. This distribution shows that more than four fifths of the patients have increased body weight or obesity, which represent a significant cardiometabolic risk factor in the context of peripheral artery disease and diabetes mellitus type 2. Summarized the study included a total of 230 patients with a relatively even distribution according to age and average age of 64,44 years. In relation to the anthropometric characteristics the average BMI is 28,96 kg/m2 and the largest part of patients are in the category of overweight or obesity. The analysis demonstrates that overweight and obesity were common among patients with PAD, particularly among those with T2DM. Obesity is more connected to the metabolic profile in patients with elevated HbA1c levels. The findings of this study are generally consistent with previous large international clinical trials and epidemiological studies. The UKPDS demonstrated that improved glycaemic control significantly reduces the risk of diabetic complications. The ADVANCE and ACCORD trials confirmed the relationship between metabolic control and cardiovascular outcomes in diabetic patients. Another clinically relevant recognition from this study is the importance of routine vascular screening and care in patients with long-standing T2DM. Many diabetic patients are asymptomatic or present with nonspecific symptoms despite significant arterial disease. Clinicians should take a high level of suspicion in patients with poor glycaemic control, dyslipidaemia, smoking history and prolonged diabetes duration. Endocrinologists, internists, vascular specialists, cardiologists and primary care physicians should work together in the early identification and treatment of vascular complications. Patient education, recognition of ischemic symptoms before they worsen and regular screening and monitoring is also very important.

Future studies with larger populations and more detailed vascular assessment are necessary to confirm the relationship between metabolic abnormalities and PAD severity in diabetic patients.

Table 3: Descriptive Statistics for Diabetes Duration

Variable	N	Mean	SD	Median	Q1	Q3	IQR	Min	Max
Duration of diabetes	200	7.94	6.8	6	3	11	3.0–11.0	0.1	32

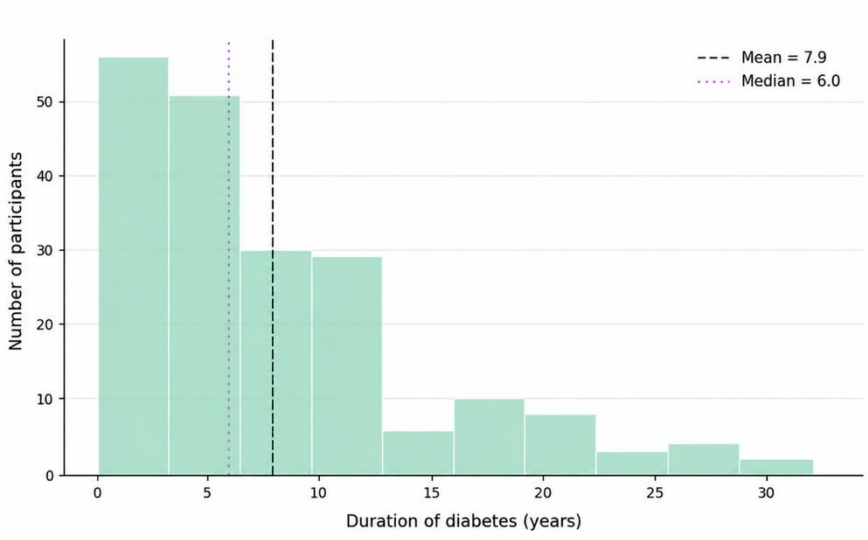


Figure 4: Distribution of Diabetes Duration

Table 4: Distribution of Participants According to Cigarette Smoking

Cigarette smoking	N	%
Yes	144	62.6
No	86	37.4

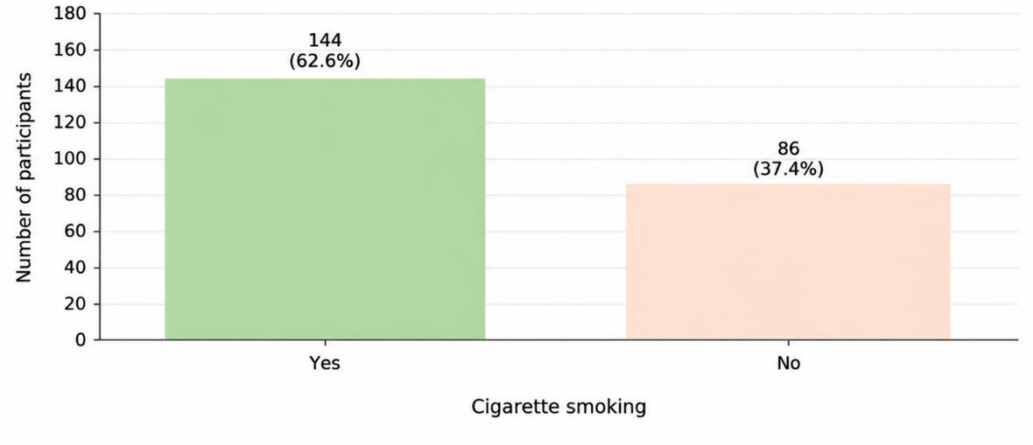


Figure 5. Distribution of Participants According to Cigarette Smoking

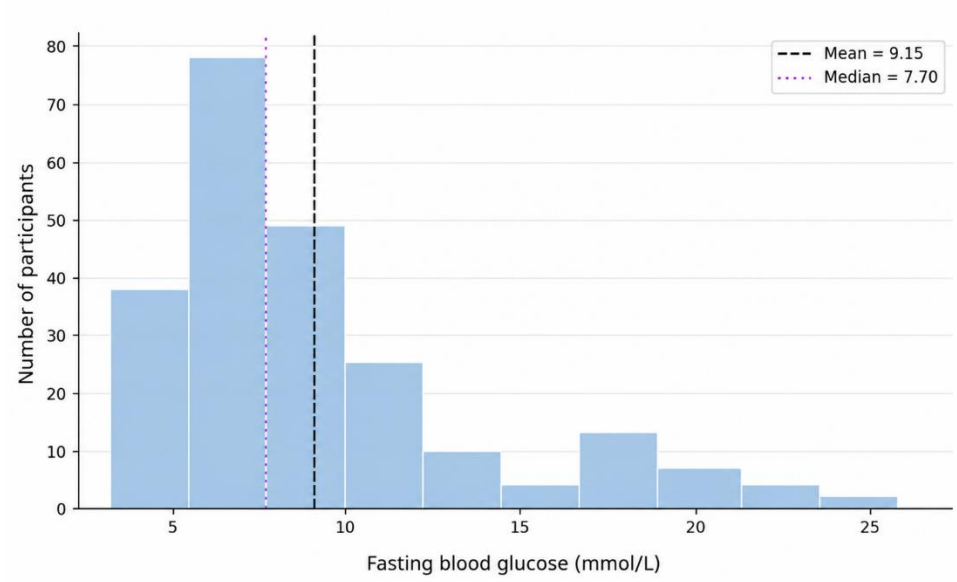


Figure 6: Distribution of Fasting Blood Glucose Levels

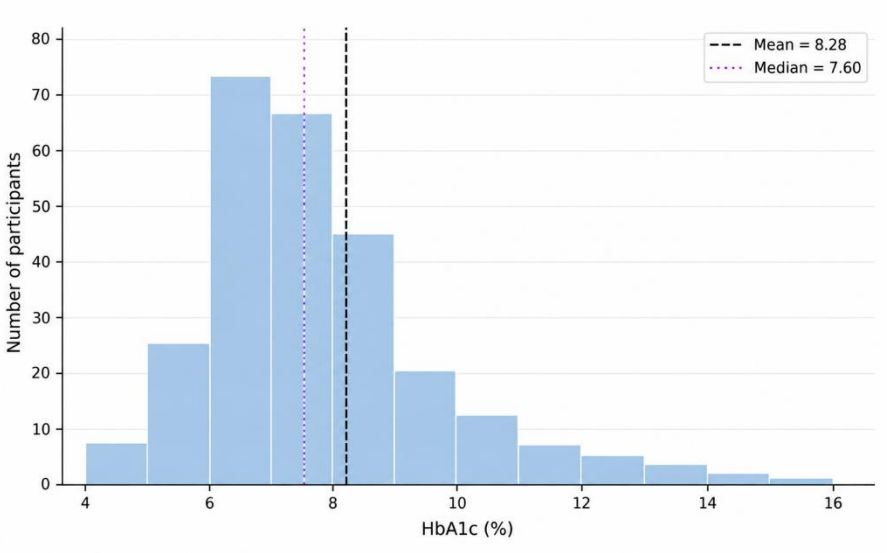


Figure 7. Distribution of HbA1c

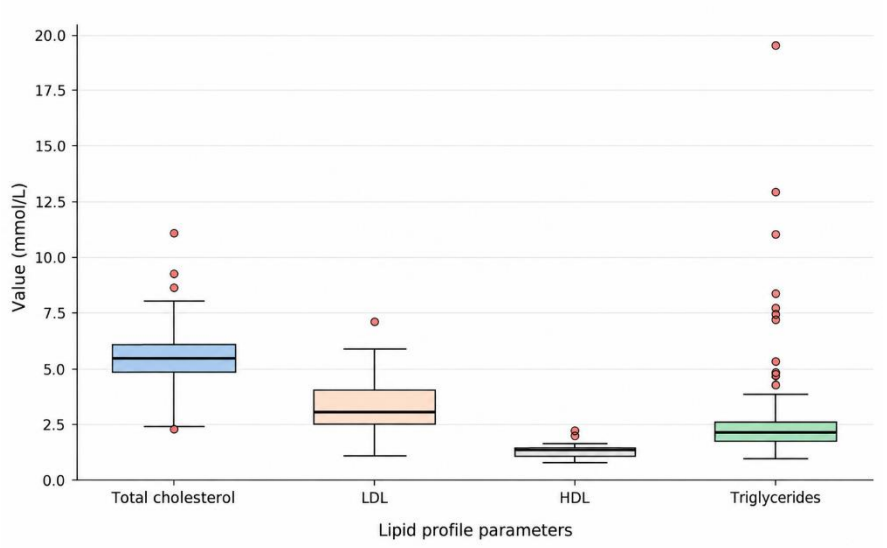


Figure 8. Distribution of Lipid Profile Parameters

Table 5. Distribution According to the Degree of Vascular Changes

Degree of vascular changes	N	%
Good finding	193	83.9
Atherosclerotic plaques	17	7.4
Significant stenosis	20	8.7

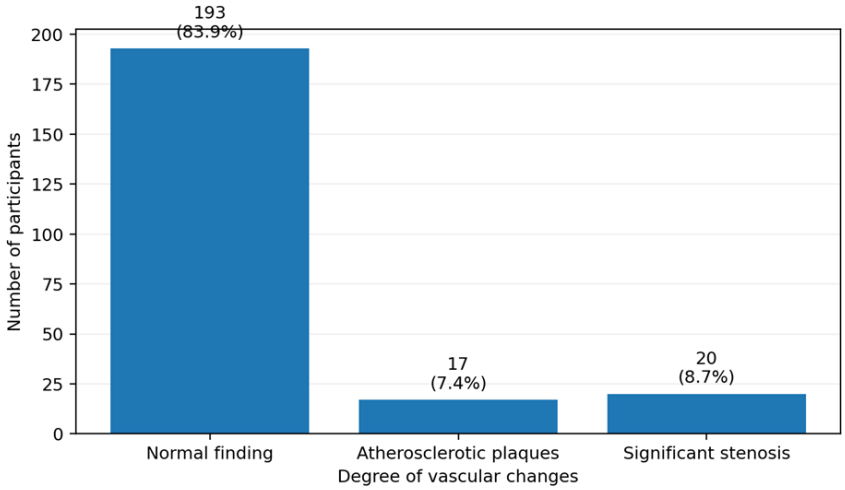


Figure 9. Distribution According to the Degree of Vascular Changes

In relation to the degree of vascular changes in the largest part of the patients' a good result was registered and in the less clinically significant part there are structural vascular changes like atherosclerotic plaques or significant stenosis.

Discussion

This study demonstrated that poor glycaemic control and unfavourable lipid profile are associated with increased symptoms suggestive of peripheral arterial disease in patients with type 2 diabetes mellitus. Patients with elevated HbA1c values showed significantly higher prevalence of intermittent claudication, lower limb pain, numbness, cold extremities, and reduced walking distance. These findings indicate that chronic hyperglycaemia and dyslipidaemia may contribute to vascular impairment and peripheral ischemia [2, 10, 13]. The relatively high prevalence of PAD-associated symptoms was observed in this study. The importance of routine vascular assessment in diabetic patients, particularly in those with prolonged duration of diabetes and poor metabolic control is evident. Chronic exposure to elevated blood glucose levels promotes endothelial dysfunction, oxidative stress, inflammation and accelerated atherosclerosis increasing the risk of ischemic complications [2, 13, 16]. Our findings are consistent with previous studies demonstrating that poor glycaemic control is strongly associated with progression of macrovascular complications in diabetic patients. The UKPDS, ADVANCE and ACCORD trials all confirmed the importance of metabolic regulation in reducing cardiovascular and vascular complications [7-9]. The most studies demonstrated that dyslipidaemia and smoking are major risk factors to PAD development in patients with T2DM.

The significantly elevated LDL cholesterol and triglyceride values observed in patients with higher HbA1c support the relationship between dyslipidaemia and vascular disease progression. PAD is a major cause of lower extremity amputation and is strongly associated with increased cardiovascular morbidity and mortality [18, 19]. In diabetic patients, PAD often can be misdiagnosed because symptoms may be masked by diabetic neuropathy or reduced physical activity. Early identification of vascular symptoms is critically important in routine clinical practice. Another important aspect seen in this study is the need for cardiovascular risk reduction strategies in patients with T2DM. Optimization of glycaemic control, lipid-lowering therapy, smoking cessation, blood pressure regulation, weight management and physical activity should all be considered as essential components of diabetic care. Early intervention

may significantly reduce progression of vascular disease and improve patient outcomes [23-25].

Conclusion

Early screening with Doppler ultrasonography and optimization of glycaemic and lipid parameters in patients with type 2 diabetes mellitus may reduce the risk of macrovascular complications such as peripheral arterial disease and improve patient outcomes. Patients with poor glycaemic control and dyslipidaemia have higher prevalence of symptoms associated with peripheral arterial disease. The findings of this study support the importance of metabolic control as a key strategy in prevention and early recognition of PAD-related symptoms in patients with T2DM. Doppler ultrasonography is useful, safe and should be used more often to screen patients with unfavourable metabolic profile and symptoms associated with peripheral arterial disease. The multidisciplinary management may lead to earlier diagnosis, improved vascular outcomes and reduce the long-term diabetic complications.

References

[1]. American Diabetes Association. Standards of care in diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S1-S350.
[2]. Beckman JA, Creager MA. Vascular complications of diabetes. Circ Res. 2016; 118(11):1771-1785.
[3]. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015; 116(9):1509-1526.
[4]. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease. Circulation. 2017;135:e726-e779.
[5]. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. J Vasc Surg. 2000; 31:S1-S296.
[6]. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care. 2003; 26(12):3333-3341.
[7]. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment. Lancet. 1998; 352:837-853.
[8]. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358:2560-2572.
[9]. ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358:2545-2559.
[10]. Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes—a review. Diabet Med. 2010; 27(1):4-14.
[11]. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States. Circulation. 2004; 110:738-743.
[12]. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease. Lancet. 2013; 382:1329-1340.
[13]. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease. Circulation. 2003; 108:1527-1532.
[14]. Hiatt WR, Armstrong EJ, Larson CJ, Brass EP. Pathogenesis of the limb manifestations and exercise limitations in peripheral artery disease. Circ Res. 2015; 116(9):1527-1539.
[15]. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021.
[16]. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. N Engl J Med. 2005; 352(5):487-497.
[17]. Aronow WS, Ahn C. Prevalence of peripheral arterial disease in elderly patients with diabetes mellitus. Diabetes Care. 1994; 17(6):595-597.
[18]. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: Hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care. 2002; 25(5):894-899.
[19]. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004; 141(6):421-431.

[20]. Betteridge DJ. Diabetic dyslipidemia and vascular disease. Diabetes Obes Metab. 2000; 2(Suppl 1):S31-S36.
[21]. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in high-risk individuals. Lancet. 2002; 360:7-22.
[22]. Boulton AJM. Diabetic neuropathy and foot complications. Handb Clin Neurol. 2014; 126:97-107.
[23]. American Heart Association. Lifestyle interventions and cardiovascular risk reduction in diabetes mellitus. Circulation. 2015; 132:691-718.
[24]. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline. J Vasc Surg. 2016; 63(2 Suppl):3S-21S.
[25]. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: pathophysiology, clinical consequences and medical therapy. Eur Heart J. 2013; 34(31):2436-2443.