Journal of Diabetes and Its Complications 38 (2024) 108871

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.elsevier.com/locate/jdiacomp

Association between Mediterranean diet adherence and peripheral artery disease in type 2 diabetes mellitus: An observational study

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ARTICLE INFO

Keywords:
Type 2 diabetes mellitus
Peripheral arterial disease
Mediterranean diet
Diabetic foot ulcer
Intermittent claudication
Amputation

ABSTRACT

Introduction: To evaluate the relationship between adherence to the Mediterranean diet (MD) and periphereal artery disease (PAD) in patients with type 2 diabetes mellitus (T2DM).
Methods: An observational sectional study was conducted with 174 patients diagnosed with T2DM, of which 78 patients had PAD. A patient was considered to have PAD if they obtained an ankle-brachial index (ABI) < 0.9 and/or absence of both distal pulses in one of the two feet. Data on sociodemographic and anthropometric variables, physical activity, smoking habits, biochemical blood parameters, and comorbidities were recorded. Good adherence to the MD was considered with a score ≥ 9 in MEDAS-14. Vascular factors independently associated with adherence to the MD in patients with T2DM were identified through multivariate logistic regression analysis.
Results: ABI, DFU, intermittent claudication and pedal pulse absence correlated with MD adherence. DFU, intermittent claudication and posterior tibial pulse absence were associated with the final score obtained in the MEDAS-14. Nut consumption, white meat preference and sautéed dish intake were associated with PAD presence. Multivariate analysis linked MD adherence to sex (OR = 0.044, 95 % CI 0.003–0619), age (OR = 0.139, 95 % CI 0.029–0.666), duration of T2DM (OR = 7.383, 95 % CI 1.523–35.779) and age at diagnosis of T2DM (OR = 6082, 95 % IC 1.415–26.136), as well as the presence of DFU (OR = 0.000, 95 % IC 0.000–0.370) and intermittent claudication (OR = 0.004, 95 % IC 0.000–0.534).
Conclusions: Adherence to the MD is associated with a reduction in vascular complications in T2DM, highlighting its potential as a dietary intervention strategy.

1. Introduction

Diabetes mellitus (DM) is a chronic disease and a major public health problem due to its high and rising prevalence. In 2021, the global prevalence of DM in adults was around 10.5 %, but this figure is projected to increase to 12.2 % by 2045.[1] Type 2 Diabetes Mellitus (T2DM) represents 90–95 % of all DM cases.[2]

The World Health Organization (WHO) defines diabetic foot (DF) as the "ulceration, infection, and/or gangrene of the foot, associated with diabetic neuropathy and varying degrees of peripheral artery disease (PAD) resulting from the complex interaction of different factors induced by sustained hyperglycaemia".[3]

PAD is an obstructive atherosclerotic vascular disease of the arteries, causing disorders or alterations in circulation in the lower extremities.[4] Its prevalence in the general population is around 10–26 %, but in the diabetic population, this can rise to 50 %, intensifying with the duration and progression of the disease.[5] While typical symptoms include intermittent claudication, diabetic patients may exhibit atypical presentations due to neuropathy and sedentary lifestyles.[6] PAD is associated with an increased risk of adverse cardiovascular events and amputation

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https://doi.org/10.1016/j.jdiacomp.2024.108871
Received 20 June 2024; Received in revised form 5 September 2024; Accepted 15 September 2024
Available online 23 September 2024

of the lower limb.[6] The mortality associated with DM-related amputations exceeds that of cancer,[7] and in 85 % of cases, it is preceded by a diabetic foot ulcer (DFU), subsequently complicated by gangrene and infection.[8] The annual treatment cost in the USA for patients presenting simultaneous PAD and DM ranges from 84 to 381 billion dollars.[9]

The Mediterranean Diet (MD) was recognized as an Intangible Cultural Heritage of Humanity by the United Nations Educational, Scientific, and Cultural Organization (UNESCO) in 2010.[10] This diet is based on the consumption of foods from traditional agriculture, including fresh fruit, vegetables, whole grains, legumes, nuts and olive oil, with a moderate intake of poultry, fish, dairy products and red wine, and a reduced intake of red meat and sweets.[11]

The MD plays a crucial role in the prevention of T2DM. It has been demonstrated to reduce the risk of developing T2DM,[12–15] delay the need for antidiabetic medications,[16] and even achieve disease remission.[17] This dietary regimen is also linked to a lower incidence of microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy.[18] A recent study indicated that reduced adherence to this diet is associated with more significant impairments in pressure sensitivity, as measured by the monofilament test.[19]

Moreover, the MD is recognized as an effective tool for primary prevention of cardiovascular events.[20] Adherence to the MD can inhibit the development of atherosclerosis, being associated with a lower incidence of atheromatous plaques due to the antioxidant effect of essential components such as fruits, vegetables and nuts.[21] It also reduces the mortality associated with cardiovascular diseases,[22] including coronary artery disease, cerebrovascular diseases, heart failure and PAD. Finally, a healthy lifestyle is associated with a reduced risk of PAD in a high cardiovascular risk population, such as patients with T2DM.[23]

While the relationship between the MD and vascular involvement is known, its association with foot artery lesions and the presence of ulcers and amputations remains unclear. To evaluate the relationship between the adherence to the MD and PAD in patients with T2DM.

2. Materials and methods

2.1. Study design

This observational descriptive cross-sectional study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was performed according to the Declaration of Helsinki (2008) and approved by the Ethics Committee for Research with Medicines of the Alicante Health Department — General Hospital, reference CEIm P12019-106. All patients included in the study signed the informed consent.

2.2. Study setting and sampling

Conduced at an endocrinology outpatient clinic of the Hospital General Universitario Dr. Balmis and a primary healthcare clinic of Centro de Salud San Blas in Alicante, Spain, from December 2020 to July 2023.

A sample size of 174 (157 + 10 % losses) subjects was estimated for the reference population, assuming an estimated prevalence of MD adherence of 82%,[24] with a 95 % confidence level, a precision of 6 % and 10 % losses.

We initially identified 196 potentially eligible participants. Out of these, 174 were ultimately included in the study. We were unable to include 22 participants due to various reasons: 12 could not be contacted to schedule their participation, 3 had passed away, and 7 declined to provide informed consent.

All patients who attended the clinic and met the inclusion and exclusion criteria were consecutively included in the study, regardless of the reason for their visit. This included initial consultations, follow-up visits, and appointments specifically for diabetic foot ulcer care.

2.3. Inclusion and/or exclusion criteria

The following inclusion criteria were applied: patients diagnosed with T2DM with >5 years of evolution, aged at least 18 years, whose native language was Spanish, and who agreed to participate in the study. The exclusion criteria were: patients with a life expectancy of <6 months; who had suffered amputation of both lower limbs; who presented neuropathy with an aetiology other than DM; and who presented cognitive impairments or mental illnesses that would preclude comprehension of the questionnaire.

2.4. Data collection

Sociodemographic variables (gender, age, nationatily, marital status ("not married" included individuals who are single, separated, widowed, or in another unspecified category), level of education and type of family cohabitation) were obtained via a clinical interview. T2DM was characterised by disease duration and age at diagnosis, based on data collected from the electronic health records. Smoking habits were assessed by identifying each participant as a non-smoker, ex-smoker, or smoker, and by the number of years smoking or since quitting. Physical activity habits were also recorded (a patient was considered physically active if they engaged in at least 150 min of physical exercise per week, following WHO recommendations). Patient weight (kg) and height (cm) were measured using a Bamed® scale with a stadiometer. Body mass index (BMI) was calculated using the formula: weight (kg)/height^2 (m), and patients were classified in accordance with WHO criteria as presenting normal weight (BMI 18.50–24.99), overweight (BMI 25–29.9) or obesity (BMI $\geq$ 30).

Metabolic control level was assessed with a blood test performed in the six months prior to inclusion in the study, considering the values on basal blood glucose (mg/dl), glycated haemoglobin (HbA1c) (%), triglycerides (mg/dl), total cholesterol (mg/dl), HDL cholesterol (mg/dl), and LDL cholesterol (mg/dl). Metabolic control was considered inadequate if the values did not meet the American Diabetes Association (ADA) recommendations: fasting blood glucose 80–130 mg/dl, HbA1c < 7 %, triglycerides <150 mg/dl, total cholesterol <100 mg/dl, HDL cholesterol >40 mg/dl for men and >50 mg/dl for women, and LDL cholesterol <70 mg/dl. Comorbidities were established through patient-reported complications.

Palpation of the pedal pulse was performed on the dorsum of the foot, on the lateral part of the long extensor tendon of the first toe, between the second and third cuneiforms. The posterior tibial pulse was assessed behind and below the medial malleolus and classified as present or absent. When pulses could not be assessed due to significant oedema in the lower limbs or when amputation prevented palpation, they were considered absent. The presence of intermittent claudication was assessed by asking the patient if they experienced pain in the calf area while walking, which disappeared with rest.

The Ankle-Brachial Index (ABI) was calculated using a bidirectional Doppler probe BIDOP V3 (Hadeco®) and a manual sphygmomanometer (Riester®). The ABI was obtained with the patient in a supine position on a bed after a period of rest. The cuff was placed at the calf level, 2 cm above the malleolus. After applying ultrasound gel to the pedal and posterior tibial arteries, the Doppler probe was placed at a 40–60° angle to the skin, making slow movements until the highest-quality sound was located. The cuff was inflated to 30 mmHg above the pressure at which the pulsatile sound disappeared, and it was slowly deflated until the sound returned, when the systolic blood pressure (SBP) was recorded. After 1 min of rest, the measurement was performed on the other artery of the same foot. The same procedure was then carried out on the brachial artery of both arms, placing the cuff around the upper part of the arm.[4]

Two SBP values were obtained in the pedal and posterior tibial arteries of each lower limb. The highest value was selected as the reference for each limb. This value was then divided by the brachial SBP of the control arm (the one with the highest value), resulting in two ABI values, one for each lower limb. These were classified as: ischaemia <0.9, normal 0.9–1.4, possible arterial calcification >1.4, and not assessable.

In addition, the ABI values obtained were classified as either normal or pathological due to medial layer calcification of the arteries in the lower limbs (Mönckeberg sclerosis). The latter condition is present in most PAD and DFU patients, associated with autonomic peripheral neuropathy, resulting in elevated ABI values.[4] Therefore, it was deemed appropriate to consider an ABI value as pathological when it was <0.9 or >1.4. If the ABI was not assessable due to significant oedema, phlebitis, lymphangitis, suspected superficial or deep vein thrombosis, venous ulcer presence, or lower limb amputations preventing determination, it was also considered altered.

Adherence to the MD was assessed with the MEDAS-14 questionnaire used in the PREDIMED study.[25] This instrument consisting of 14 items concerning the frequency of consumption of foods considered characteristic of the MD (olive oil, nuts, vegetables, fruits, fish and legumes). The final score was obtained by summing the 14 items, with an affirmative response scoring one point and a negative response scoring zero points. A score of 9 points or more on this scale was considered to represent good adherence to the MD.[26,27]

2.5. Statistical analysis

Statistical analysis of the study data was conducted using the Statistical Package of Social Sciences (SPSS®) v.28. The qualitative variables were described by frequency distributions (counts and percentages), and the quantitative ones, by means and standard deviations or median and quantiles if normality could not be assumed. Normality was assessed with the Shapiro-Wilk test (n < 50) or Kolmogorov-Smirnov test (n ≥ 50). Bivariate inferential analysis was conducted to identify associated risk factors, calculating the corresponding odds ratio and applying statistical tests such as chi-square or Fisher's exact test for the qualitative variables, and Student's *t*-test for independent samples or the Mann-Whitney *U* test for quantitative variables, according to conditions of application. To identify the factors that are independently associated with adherence to the MD in patients with PAD, we obtained the adjusted odds ratio (OR) and confidence interval (CI) through a multivariate logistic regression analysis. All variables that showed a significant association in the bivariate analysis were included in the multivariate analysis, along with those variables that were considered relevant according to the scientific literature. Results were considered statistically significant when the *p*-value was <0.05.

3. Results

A total of 174 patients with T2DM were included in the study. Of these, 61.5 % were male and 38.5 % female, with an average age of 69.56 ± 8.86 years (95 % CI 68.23–70.88). The mean BMI was 29.57 ± 4.74 (95 % CI 28.86–30.28), with 41.4 % of the participants presenting with overweight and 43.1 % with obesity. The nationality of the patients was 97.7 % Spanish, 1.1 % Algerian, 0.6 % French, and 0.6 % Cuban. 98.9 % of the patients is of Caucasian ethnicity.

The average duration of T2DM among these patients was 15.34 ± 9.83 years (95 % CI 13.87–16.81), and the mean age at diagnosis was 54.32 ± 11.32 years (95 % CI 52.63–56.02). Approximately 55.1 % of the patients had no formal education or had completed only primary education.

A sedentary lifestyle was reported by 37.9 % of participants, and 15.5 % were smokers during the study, with an average tobacco consumption duration of 44.75 ± 13.20 years (95 % CI 39.63–49.87). Of the participants, 52.3 % had a prior history of smoking, with an average duration since quitting of 19.01 ± 13.27 years (95 % CI 16.25–21.77).

Regarding the treatment of patients with T2DM, 3.4 % were managed exclusively with diet and exercise. A total of 59.8 % were treated with oral antidiabetic drugs, 3.4 % with insulin, and 0.6 % with GLP-1 analogs. Additionally, 32.2 % of patients received a combination of oral antidiabetic drugs with another treatment (either insulin or GLP-1 analogs), and 0.6 % were treated with a combination of insulin and GLP-1 analogs.

In Table 1, the patients with PAD presented a longer duration of T2DM (18.56 ± 10.41 vs. 12.72 ± 8.52; $p < 0.001$), lower age at diagnosis (51.46 ± 12.8 vs 56.65 ± 9.39; $p = 0.007$) and lower levels of education ($p = 0.033$), and of physical activity ($p < 0.001$), compared to the patients without PAD.

Regarding the T2DM control parameters considered, the values obtained for LDL cholesterol (69.8 %), basal blood glucose (56.3 %), and HbA1c (42.5 %) were the ones most frequently not meeting the recommendations of the ADA. Among associated comorbidities, dyslipidaemia (82.8 %) was most frequently observed, followed by hypertension (77 %) and cardiac problems (31 %).

In Table 2, the values found to be significantly positive associated with PAD were HbA1c ($p = 0.016$), HDL cholesterol ($p = 0.046$) and the microalbumin-creatinine ratio ($p < 0.001$), together with the presence of coronary disease ($p = 0.003$), heart problems ($p = 0.001$), nephropathy ($p = 0.026$) and retinopathy ($p < 0.001$). Conversely, LDL cholesterol ($p = 0.032$) exhibited an inverse association with PAD. The average total cholesterol level and LDL cholesterol were significantly higher in patients without PAD compared to patients with PAD (171.58 ± 41.54 vs. 155.65 ± 48.64; $p = 0.009$ and 92.13 ± 33.55 vs. 80.85 ± 37.04; $p = 0.020$, respectively).

Concerning T2DM complications affecting the foot, 18.4 % of patients had experienced a DFU during the course of their illness (9.8 % in

Table 1
Sociodemographic characteristics of the patients with T2DM included in the study.

Sociodemographic variables	PAD n = 78 n (%) Mean ± SD Median (Q1–Q3)	No PAD n = 96 n (%) Mean ± SD Median (Q1–Q3)	*p* value
Sex			
Male	49 (62.8)	58 (60.4)	0.746
Female	29 (37.2)	38 (39.6)	
¥Age (years)	70.12 ± 9.39	69.9 ± 8.42	0.328
Marital status			
Not married	27 (34.6)	36 (37.5)	0.694
Married	51 (65.4)	60 (62.5)	
Educational level			
No formal, or only primary studies	50 (64.1)	46 (47.9)	0.033*
Secondary or university studies	28 (35.9)	50 (52.1)	
Family cohabitation			
Lives alone	12 (15.4)	19 (19.8)	0.450
Lives with someone	66 (84.6)	77 (80.2)	
BMI			
Normal weight (BMI 18.50–24.99)	15 (15.6)	12 (15.4)	0.210
Overweight (BMI 25–29.9)	45 (46.9)	27 (34.6)	
Obesity (BMI ≥ 30)	36 (37.5)	39 (50.0)	
Smoking habit			0.258
Current smoker	16 (20.5)	11 (11.5)	
Ex-smoker	38 (48.7)	53 (55.2)	
Never smoked	24 (30.8)	32 (33.3)	
Physical activity			
Sedentary lifestyle	41 (52.6)	25 (26)	<0.001*
Physically active	37 (47.4)	71 (74)	
¥Duration of T2DM (years)	18.56 ± 10.41 17 (10.8–25)	12.72 ± 8.52 11 (6–17)	<0.001*
¥Age at T2DM diagnosis (years)	51.46 ± 12.8	56.65 ± 9.39	0.007*

Chi-squared test. SD, standard deviation; Q1, quartile 1; Q3, quartile 2. BMI, body mass index; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus.

¥ Mann-Whitney *U* test.

* $p < 0.05$ statistically significant.

Table 2
Metabolic control parameters and comorbidities of the patients with T2DM included in the study.

Metabolic control parameters and comorbidities	PAD n = 78 n (%) Mean ± SD	No PAD n = 96 n (%) Mean ± SD	*p* value
[¥]Basal blood glucose (mg/dl)	137.67 ± 39.9	137.02 ± 40.64	0.558
Normal (80–130 mg/dl)	32 (41)	44 (45.8)	0.525
Altered (<80 to >130 mg/dl)	46 (59)	52 (54.2)	
[¥]Hb1Ac (%)	7.19 ± 1.2	6.95 ± 1.14	0.088
Normal (<7 %)	37 (47.4)	63 (65.6)	0.016*
Altered (≥7 %)	41 (52.6)	33 (34.4)	
[¥]Triglycerides (mg/dl)	146.17 ± 97.25	153.57 ± 77.24	0.186
Normal (<150 mg/dl)	52 (66.6)	60 (62.5)	0.568
Altered (≥150 mg/dl)	26 (33.3)	36 (37.5)	
[¥]Total cholesterol (mg/dl)	155.65 ± 48.64	171.58 ± 41.54	0.009*
Normal (<100 mg/dl)	63 (80.8)	77 (80.2)	0.926
Altered (≥100 mg/dl)	15 (19.2)	19 (19.8)	
[¥]LDL cholesterol (mg/dl)	80.85 ± 37.04	92.13 ± 33.55	0.020*
Normal (<70 mg/dl)	28 (38.9)	21 (23.3)	0.032*
Altered (≥70 mg/dl)	44 (61.1)	69 (76.7)	
[¥]HDL Cholesterol (mg/dl)	47.90 ± 16.88	49.09 ± 12.25	0.166
Normal (men > 40 mg/dl; women > 50 mg/dl)	40 (56.3)	65 (71.4)	0.046*
Altered (men ≤ 40 mg/dl; women ≤ 50 mg/dl)	31 (43.7)	26 (28.6)	
[¥]Creatinine (mg/dl)	1.35 ± 1.66	1.01 ± 0.95	0.188
Normal (men ≤ 1.2 mg/dl; women ≤ 1.1 mg/dl)	62 (79.5)	86 (89.6)	0.063
Altered (men > 1.2 mg/dl; women > 1.1 mg/dl)	16 (20.5)	10 (10.4)	
[¥]Microalbumin-creatinine ratio (mg/g)	113.98 ± 188.05	35.29 ± 74.16	<0.001*
Normal (<30 mg/g)	41 (54.7)	79 (82.3)	<0.001*
Altered (≥30 mg/g)	34 (45.3)	17 (17.7)	
[¥]Glomerular filtration rate (ml/min)	62.9 ± 22.3	70.94 ± 15.85	0.062
Normal (≥60 ml/min)	56 (71.8)	80 (83.3)	0.067
Altered (<60 ml/min)	22 (28.1)	16 (16.7)	
Coronary heart disease			
No	55 (70.5)	85 (88.5)	0.003*
Yes	23 (29.5)	11 (11.5)	
Hypertension			
No	17 (21.8)	23 (24)	0.736
Yes	61 (78.2)	73 (76)	
Cerebrovascular disease			
No	68 (87.2)	88 (91.7)	0.334
Yes	10 (12.8)	8 (8.3)	
Heart problems			
No	44 (56.4)	76 (79.2)	0.001*
Yes	34 (43.6)	20 (20.8)	
Dyslipidaemia			
No	15 (19.2)	15 (15.6)	0.531
Yes	63 (80.8)	81 (84.4)	
Nephropathy			
No	48 (61.5)	74 (77.1)	0.026*
Yes	30 (38.5)	22 (22.9)	
Retinopathy			
No	41 (52.6)	84 (87.1)	<0.001*
Yes	37 (47.4)	12 (12.5)	
Cancer			
No	61 (78.2)	77 (80.2)	0.746
Yes	17 (21.8)	19 (19.8)	
Depression			
No	59 (75.6)	73 (76)	0.951
Yes	19 (24.4)	23 (24)	
[¶]Dialysis			
No	75 (96.2)	96 (100)	0.088
Yes	3 (3.8)	0 (0)	
Lung disease			
No	50 (64.1)	72 (75)	0.118
Yes	28 (35.9)	24 (25)	

Chi-squared test. SD, standard deviation; Hb1Ac, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus.
[¶] Fisher's exact test.
[¥] Mann-Whitney *U* test.
[*] $p < 0.05$ statistically significant.

the right foot and 10.9 % in the left foot), presenting ulcers in both feet in 2.3 % of cases. Among patients with ulcers, we found that 25 % had suffered amputations, with 9.4 % of those cases being amputations of both feet.

DFU were observed in 35.9 % of the patients with PAD and in 4.2 % of the patients without PAD (OR 12.88, 95 % CI 4.275–38.802; $p < 0.001$). 78.6 % of the patients with PAD and 21.4 % of the patients without PAD had suffered lower limb amputation (OR 5.09 (95 % CI 1.36–18.95; $p = 0.008$). A DFU developed during the course of the disease among 80.6 % of the patients with PAD and 19.4 % of the patients without PAD (OR 7.53, 95 % CI 3.072–18.434; $p < 0.001$). All of these outcomes were significantly associated with the presence of PAD.

Pedal pulse was absent or non-assessable in the right foot of 15.5 % of the patients, and in the left foot in 21.3 %. This value was altered in one foot in 25.9 % of patients. The posterior tibial pulse was not palpable in the right foot of 30.4 % of patients and in the left foot of 26.4 %. This value was altered in one foot in 33.9 % of the patients. Intermittent claudication in at least one limb was present in 17.2 % of patients.

The ABI results indicated that 14.4 % of patients had PAD in the right limb, with a mean value of 1.12 ± 0.25 (95 % CI 1.07–1.16), and 10.3 % in the left limb, with a mean value of 1.15 ± 0.24 (95 % CI 1.11–1.19). Furthermore, 49.4 % of patients exhibited a pathological ABI.

In Table 3, the presence of DFU ($p = 0.011$), intermittent claudication ($p = 0.020$), absent pedal pulse ($p = 0.045$) and ABI ($p = 0.015$) were significantly associated with poorer adherence to the MD. Moreover, the presence of DFU (6.44 ± 1.54 vs. 7.19 ± 1.72; $p = 0.032$), intermittent claudication (6.41 ± 1.40 vs. 7.18 ± 1.74; $p = 0.029$), and

Table 3
Observed prevalences of PAD clinic and its relationship with MEDAS-14 score and adherence and non-adherence to the MD.

PAD clinical variables	MEDAS-14 score mean ± SD	[¥]*p* value	Adherence to MD (≥9 score) n = 33 n (%)	Non-adherence to MD (<9 score) n = 141 n (%)	[¶]*p* value
DFU					
No	7.19 ± 1.72	0.032*	32 (22.5)	110 (77.5)	0.011*
Yes	6.44 ± 1.54		1 (3.1)	31 (96.9)	
Amputation					
No	7.10 ± 1.73	0.203	33 (20.6)	127 (79.4)	0.075
Yes	6.50 ± 1.35		0 (0.0)	14 (100.0)	
Intermittent claudication					
No	7.18 ± 1.74	0.029*	32 (22.1)	113 (77.9)	0.020*
Yes	6.41 ± 1.40		1 (3.4)	28 (96.6)	
Pedal pulse					
Present	7.10 ± 1.77	0.389	29 (22.5)	100 (77.5)	0.045*
Absent	6.89 ± 1.54		4 (8.9)	41 (91.1)	
Posterior tibial pulse					
Present	7.23 ± 1.74	0.048*	26 (22.6)	89 (77.4)	0.087
Absent	6.69 ± 1.60		7 (11.9)	52 (88.1)	
ABI					
Normal	7.29 ± 1.63	0.069	23 (26.1)	65 (73.9)	0.015*
Pathological	6.80 ± 1.77		10 (11.6)	76 (88.4)	

Chi-squared test. ABI, ankle-brachial index; DFU, diabetic foot ulcer; MD, Mediterranean diet; MEDAS, Mediterranean Diet Adherence screener; PAD, peripheral artery disease.
[¥] U-Mann Whitney test.
[¶] Fisher's exact test.
[*] $p < 0.05$ statistically significant.

the absence of the posterior tibial pulse (6.69 ± 1.60 vs. 7.23 ± 1.74; p = 0.048) were significantly associated with lower scores on the MEDAS-14 questionnaire.

Only 12.8 % of patients with PAD adhered to the MD compared to 24 % of patients without PAD (p = 0.062). Additionally, patients with PAD had lower MEDAS-14 scores compared to those without PAD (6.86 ± 1.66 vs. 7.20 ± 1.74; p = 0.166).

In Table 4, the scores obtained for each questionnaire item revealed significant associations with lower PAD observed in those who consumed nuts at least 3 times a week (OR = 0.44, 95 % CI 0.232–0.848; p = 0.013) and sautéed food at least twice a week (OR = 0.45, 95 % CI 0.226–0.896; p = 0.022).

Finally, Table 5 shows that the multivariate analysis revealed that male sex (OR = 0.044, 95 % CI 0.003–0619), older age (OR = 0.139, 95 % CI 0.029–0.666), the presence of DFU (OR = 0.000, 95 % IC 0.000–0.370), and intermittent claudication (OR = 0.004, 95 % IC 0.000–0.534) were associated with poorer adherence to the MD. In contrast, a longer duration of T2DM (OR = 7.383, 95 % CI 1.523–35.779) and an older age at diagnosis (OR = 6.082, 95 % IC 1.415–26.136) were associated with greater adherence to the MD.A Nagelkerke R^2 value of 0.65 was obtained, which indicates that approximately 65 % of the variability in adherence to the MD among the study participants can be explained by the variables included in the model. This suggests a strong explanatory power of the model in identifying factors associated with dietary adherence.

4. Discussion

The objective of this observational study was to assess the relationship between adherence to the MD and PAD in patients with T2DM.

Individuals with PAD exhibited a longer duration of T2DM, an earlier age at T2DM diagnosis, lower levels of education and reduced physical activity.[29] Our study identified significant association between between PAD and altered levels of HbA1c, HDL cholesterol and the microalbumin-creatinine ratio. Notably, total cholesterol and LDL cholesterol were higher in patients without PAD. These results coincide with those of a prospective study by Adler et al.[28] and Bertrand et al.[29] The higher cholesterol levels in patients without PAD might be due to elevated triglyceride levels in the sample, which could have affected the laboratory measurement of LDL. Additionally, patients with PAD may have been receiving more aggressive antihyperlipidemic treatment for secondary prevention.

In addition to associations with metabolic risk factors, our results also indicated a significant association between PAD and coronary

Table 5
Logistic regression to determine the factors associated with adherence to the MD in patients with PAD.

Variable	Categories	Adjusted OR 95 %	CI
Sex	Female	1	
	Male	0.044	0.003–0.619
Age (years)		0.139	0.029–0.666
Duration of T2DM (years)		7.383	1.523–35.779
Age at T2DM diagnosis (years)		6.082	1.415–26.136
DFU	No	1	0.000–0.370
	Yes	0.004	
Amputation	No	1	0.000
	Yes	0.000	
Intermittent claudication	No	1	0.000–0.534
	Yes	0.004	
Pedal pulse	Present	1	0.101–29.056
	Absent	1.717	
Posterior tibial pulse	Present	1	0.490–439.564
	Absent	14.677	
ABI	Normal	1	0.333–944.830
	Pathological	17.744	

Dependent variable: Adherence to the MD (≥9 score).
ABI, ankle-brachial index; CI, confidence interval; DFU: diabetic foot ulcer; MD: Mediterranean diet; T2DM, type 2 diabetes mellitus.

Table 4
Distribution of dietary components in the MEDAS-14 in PAD and no PAD.

MEDAS-14	Category	PAD n = 78 n (%)	No PAD n = 96 n (%)	OR	95 % IC	p value
Question 1. Olive oil as the primary fat	Yes	68 (87.2)	91 (94.8)	0.374	0.122–1.14	0.075
	No	10 (12.8)	5 (5.2)			
Question 2. Olive oil (quantity)	≥4 tablespoons a day	34 (43.6)	42 (43.8)	0.994	0.544–1.815	0.983
	<4 tablespoons a day	44 (56.4)	54 (56.3)			
Question 3. Vegetables	≥Twice a day	11 (14.1)	13 (13.5)	1.048	0.441–2.49	0.915
	<Twice a day	67 (85.9)	83 (86.5)			
Question 4. Fruit	≥3 times a day	34 (43.6)	39 (40.6)	1.129	0.617–2.068	0.693
	<3 time a day	44 (56.4)	57 (59.4)			
Question 5. Red meat	<1 time a day	71 (91)	86 (89.6)	1.179	0.427–3.257	0.750
	>1 time a day	7 (9)	10 (10.4)			
Question 6. Butter, margarine or cream	<1 time a day	68 (87.2)	82 (85.4)	1.161	0.485–2.779	0.737
	>1 time a day	10 (12.8)	14 (14.6)			
Question 7. Sugary or carbonated drinks	<1 time a day	59 (75.6)	61 (63.5)	1.782	0.918–3.459	0.086
	>1 time a day	19 (24.4)	35 (36.5)			
Question 8. Wine	≥7 times a week	9 (11.5)	19 (19.8)	0.529	0.224–1.246	0.141
	<7 times a week	69 (88.5)	77 (80.2)			
Question 9. Legumes	≥3 times a week	19 (24.4)	26 (27.1)	0.867	0.437–1.721	0.683
	<3 times a week	59 (75.6)	70 (72.9)			
Question 10. Fish or seafood	≥3 times a week	16 (20.5)	25 (26)	0.733	0.359–1.497	0.373
	<3 times a week	62 (79.5)	71 (74)			
Question 11. Non-homemade baking	<Twice a week	44 (56.4)	61 (63.5)	0.743	0.403–1.368	0.339
	≥Twice a a week	34 (43.6)	35 (36.5)			
Question 12. Nuts	≥3 times a week	20 (25.6)	42 (43.8)	0.443	0.232–0.848	0.013*
	<3 times a week	58 (74.4)	54 (56.3)			
Question 13. White meat preferably	Yes	67 (85.9)	68 (70.8)	2.508	1.156–5.443	0.018*
	No	11 (14.1)	28 (29.2)			
Question 14. Sautéed dishes	≥Twice a week	16 (20.5)	35 (36.5)	0.450	0.226–0.896	0.022*
	<Twice a week	62 (79.5)	61 (63.5)			

Chi-squared test. CI, confidence interval; MEDAS, Mediterranean Diet Adherence Screener; OR, odds ratio; PAD, peripheral artery disease.
* <0.05 statistically significant.

artery disease, heart problems, nephropathy, retinopathy, DFU and amputations.[32]

Our findings also revealed an inverse correlation between the presence of DFU and adherence to the MD, as well as with the MEDAS-14 score. These results are consistent with those found in the study by Zúnica-García et al.,[30] where adherence to the MD was associated with a lower incidence of DFU in individuals with T2DM. A systematic review of this question identified lower concentrations of nutrients such as selenium, vitamins C, D, E, and B12 among patients with DFU compared to those without ulcers. All of these nutrients are commonly found in the MD,[31] with the consumption of elements such as fruits, vegetables, nuts, fish, legumes or extra virgin olive oil.

Among the dietary components evaluated by the MEDAS-14, the recommended intake of nuts and sautéed foods (tomato sauce, garlic, onion or leek, cooked slowly with olive oil) has been shown protect against the development of PAD. Specifically, the PREDIMED study[32] suggested an inverse association between this dietary intervention and the development of PAD. This study concluded that a MD supplemented with extra virgin olive oil or nuts was associated with a lower risk of PAD compared to a low-fat diet (control group). PAD is a clinical manifestation of atherosclerosis, a chronic inflammatory disease of the arterial wall. It has been demonstrated that the consumption of a MD supplemented with extra virgin olive oil and nuts, modulates the inflammatory response by reducing plasma concentrations of inflammatory biomarkers and circulating molecules associated with atheroma plaque instability. This may explain the protective effect of this diet against atherosclerosis.[33,34]

Patients with intermittent claudication, a typical symptom of this pathology, showed lower adherence to the MD and a lower MEDAS-14 score. Pedal pulse and posterior tibial pulse were more frequently absent in non-compliant MD patients and those with lower MEDAS-14 scores, respectively. A pathological ABI was associated with lower adherence to the MD. These results are similar to those obtained by Mattioli et al.[21] in a study of premenopausal women, where those deviating from MD adherence had lower ABI values compared to those adhering to it. A recent meta-analysis has highlighted the significant benefits of the MD in improving endothelial function. These benefits are postulated to be explained through various mechanisms, such as increasing nitric oxide bioavailability, crucial for endothelial health, as well as reducing LDL cholesterol oxidation and exerting anti-inflammatory effects by regulating markers like interleukin-6 and C-reactive protein, all of which are linked to endothelial dysfunction. Given the importance of endothelial dysfunction in the pathogenesis of intermittent claudication, which contributes to vasoconstriction and decreased blood flow in peripheral arteries, improving endothelial function through the MD may have significant implications in reducing symptoms associated with intermittent claudication and improving walking capacity in affected patients.[35]

Different studies suggest that interventions in nutritional education or physical activity promote a healthy lifestyle and improve adherence to the MD.[36–38] This educational approach not only facilitates better adherence to this dietary pattern but also has a positive impact on wound healing, ulcer recurrence, and mortality in individuals with DFU.[39] Therefore, implementing comprehensive therapeutic education may be crucial for optimizing adherence to the MD and, consequently, improving health outcomes in patients with PAD.

4.1. Limitations

The present study has certain limitations that should be taken into account. Firstly, sample selection was by non-probabilistic sampling, which is open to criticism. However, this technique is commonly employed in observational studies, and there is no reason to believe that the characteristics of the recruited patients differ from those of other patients who meet the selection criteria.

In addition, the patients' adherence to the MD was assessed by means of a self-completed questionnaire, beyond the researcher's direct control. Accordingly, the data recorded are subject to possible recall bias. On the other hand, this questionnaire has been previously validated.[26]

The use of the ABI may not be a completely accurate diagnostic method for PAD in high-risk diabetic individuals. This is because the high prevalence of arterial calcification in this population can lead to an overestimation of the ankle blood pressure. Additionally, the high incidence of peripheral neuropathy, often associated with medial calcification, can also affect the accuracy of the results.[40] To avoid this bias, future studies could consider using alternative measurements, such as the Toe-Brachial Index (TBI).[41] Finally, this study presents the inherent limitations of a cross-sectional study. Such a design captures data at a single point in time, providing a snapshot of the patients' condition during a specific moment in the progression of the disease. Since chronic complications of T2DM develop over time, the cross-sectional nature of this study does not allow for capturing the full evolution of these complications. This limitation restricts our ability to understand how dietary habits influence the development and progression of chronic complications. Thus, we cannot establish a cause-and-effect relationship or assess whether the reported dietary habits are part of daily consumption or the result of a recent change. Therefore, the hypotheses considered in this study should be further investigated in future prospective studies.

5. Conclusions

In conclusion, the results obtained in this study reveals a series of significant findings related to adherence to the MD and vascular complications in patients with T2DM and P. Factors such as sex, age, duration and age at diagnosis of T2DM, as well as the presence of DFU and intermittent claudication, are significantly associated with adherence to the MD. These findings highlight the importance of promoting healthy eating, especially among patients with T2DM and PAD, as a potential strategy to reduce the risk of vascular complications.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CRediT authorship contribution statement

Sara Zúnica-García: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **José F. Javier Blanquer-Gregori:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Ruth Sánchez-Ortiga:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Esther Chicharro-Luna:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization. **María Isabel Jiménez-Trujillo:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors thank all the patients who took part in this study.

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