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Original Article

The Effect of Trimetazidine Treatment in Diabetic Patients With Intermittent Claudication

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ABSTRACT

Background: Peripheral arterial disease (PAD) is a vascular condition for which many therapeutic decisions are well established; nonetheless, the potential role of trimetazidine (TMZ) in diabetic patients with PAD remains debatable and warrants further investigation.
Objective: This study aimed to determine the effect of TMZ on diabetic patients with intermittent claudication.

Methods: In this two-center prospective study, 188 diabetic patients with PAD received guideline-directed medical therapy (GDMT) with (n =93) or without (n =95) TMZ. Baseline and 6-month assessments included the 6-minute walk test (6MWT), ankle-brachial index (ABI), duplex ultrasound, and diabetic foot outcomes (P <0.05).

Results: The study included 188 diabetic patients with symptomatic PAD. Patients were divided into Group I, which received all GDMT with TMZ as part of chronic coronary syndrome treatment (93 patients), and Group II, which received all GDMT without TMZ (95 patients). All patients were evaluated at baseline and after a 6-month follow-up period for exercise performance via 6MWT, lower limb hemodynamics via ABI, and the incidence of diabetic foot requiring amputation. At the end of the follow-up period, 6MWT and ABI improved significantly from baseline findings in both groups. The TMZ group demonstrated a substantial improvement in 6MWT, a nonsignificant improvement in ABI, and a nonsignificant reduction in diabetic foot requiring amputation compared with the non-TMZ group.

Conclusions: TMZ may improve exercise performance in diabetic patients with PAD, while its role in improving limb hemodynamics or ischemia is nonsignificant and uncertain.
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KEYWORDS: Diabetic, Peripheral arterial disease, Trimetazidine, Intermittent claudication

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Peripheral arterial disease (PAD) is characterized by reduced blood flow in the lower extremity arteries, with the superficial femoral and common iliac arteries being commonly affected. [1] PAD affects over 200 million adults globally. [2] Diabetes mellitus (DM) is the primary risk factor for PAD, leading to a more than two-

fold increase in prevalence compared to the general population. Clinical manifestations of PAD in diabetic patients often differ from those observed in the general population. Foot ulcers, a common consequence of PAD in diabetic patients, can result in hyperglycemic crises, hospitalizations, diminished quality of life, and mortality. [3]

PAD is also linked to other common risk factors for atherosclerosis, such as obesity, smoking, and hypertension. [4, 5, 6] Moreover, PAD frequently coexists with other systemic atherothrombotic events like stroke, myocardial infarction, and cardiovascular mortality. [7]

The majority of patients with PAD experience limitations in exercise capacity due to claudication, a clinical manifestation resulting from an imbalance between metabolic demands and oxygen and substrate supply to the lower extremity muscles. [5] Although the presence of atherosclerotic arterial lesions in the lower extremities is the primary factor affecting oxygen and substrate delivery to skeletal muscles, the degree of exercise limitation in claudicant patients is not solely attributed to reduced blood flow. [8,9] Additional factors, such as impaired substrate utilization and reduced energy production in skeletal muscles, may further contribute to functional impairment in PAD patients. This functional decline may be exacerbated when diabetes coexists with PAD. [10, 11]

The anti-ischemic drug trimetazidine (TMZ) is frequently used in cases of chronic coronary syndrome (CCS). TMZ works by preventing cardiac fatty acid uptake, stimulating glucose oxidation, and enhancing mitochondrial metabolism through the inhibition of the long-chain 3-ketoacyl coenzyme A thiolate enzyme in mitochondria. [12] As a result, it optimizes glucose oxidation (aerobic metabolism), leading to improved myocardial and skeletal muscle energy production due to increased adenosine triphosphate (ATP) molecules. [13]

Additionally, TMZ reduces the buildup of lactic acid, proinflammatory cytokines, and other pain mediators associated with ischemic injury. [14]

Although previous studies have explored the potential use of TMZ in patients with PAD, [1,15] its role remains unclear. This study aims to clarify the role of TMZ in diabetic patients with PAD experiencing intermittent claudication symptoms.

Accordingly, the present study aimed to determine the effect of TMZ treatment in diabetic patients with intermittent claudication.

METHODS

This two-center observational cohort study included 188 patients with diabetes and peripheral arterial disease (PAD) who were recruited between December 2022 and December 2023 and followed for 6 months after enrollment. The local ethics committees at both centers approved the study protocol (FMBSUREC/06122022/Amin, December 2022; 36053/11/22, November 2022), in accordance with the World Medical Association's Declaration of Helsinki, which outlines the ethical principles governing medical research involving human participants. Written informed consent was obtained from all enrolled patients.

Included patients

We enrolled all eligible patients from the cardiology and vascular surgery departments and divided them into 2 groups. All patients were compliant with all guideline-directed medical therapy (GDMT). Group I (93 patients) comprised diabetic patients diagnosed with PAD and CCS. All patients in this group were compliant with TMZ 35 mg modified release twice per day as part of their CCS treatment for at least 4 weeks before inclusion. Group II (95 patients) comprised

diabetic patients with PAD, none of whom were taking TMZ.

All patients could walk unaided or with their habitual assistive device and had no cardiorespiratory conditions, such as unstable angina or chronic obstructive pulmonary disease (COPD), that could restrict exercise performance.

Diabetes mellitus (DM) was diagnosed based on a clinical history of pre-existing DM (indicated by insulin or oral antidiabetic drug use), a fasting plasma glucose level >126 mg/dL, a 2-hour postprandial plasma glucose level ≥200 mg/dL, a random plasma glucose level ≥200 mg/dL, or an HbA1c level ≥6.5% at any time. [16]

The included patients were symptomatic with intermittent claudication and met the following diagnostic criteria for PAD:

1. Color Doppler flow imaging of peripheral blood vessels confirmed a reduced diameter of the femoral, tibial, and dorsal arteries of the lower limb; intimal thickening; the presence of atherosclerotic plaque; and decreased blood flow velocity. [17]
2. An ankle-brachial index (ABI) <0.9. [17]
3. Grade II to III symptoms of PAD according to the Leriche-Fontaine classification. [18]

CCS was defined according to the European Society of Cardiology guidelines as one of the following [19]:

1. Asymptomatic and symptomatic patients more than 1 year after initial diagnosis or revascularization.
2. Asymptomatic and symptomatic patients with stable symptoms for less than 12 months following an acute coronary syndrome (ACS) or recent revascularization.
3. Asymptomatic subjects in whom coronary artery disease (CAD) was detected at screening using noninvasive tests.

Exclusion criteria

(1) Patients with evidence of PAD and noncompressible arteries with a high ABI >1.3.
(2) Patients unable to walk unassisted.
(3) Patients with COPD.
(4) Patients with blood diseases and coagulation disorders.
(5) Patients with acute lower limb ischemia.
(6) Patients with severe multiple organ failure, malignant tumors, or mental disorders.
(7) Symptomatic patients with heart failure of New York Heart Association (NYHA) functional class II or greater.
(8) Patients with a current diagnosis of ACS.
(9) Patients with poor compliance with medications and exercise programs.

All patients recruited for this study underwent the following assessments:

1. History taking.
2. Clinical examination to exclude any predefined exclusion criteria, with emphasis on medication history and cardiovascular risk factors.
3. ECG: performed to rule out arrhythmias or ECG changes suggestive of ACS.
4. Echocardiographic evaluation: conducted at baseline and at 6 months of follow-up to assess ejection fraction (EF).
5. Laboratory evaluation: metabolic profiles were assessed at enrollment. Patients with chronic kidney disease (CKD) were staged according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for evaluation and management of CKD. [20]

1. Lower limb hemodynamics

Patients underwent ABI evaluation at enrollment (baseline) and after 6 months.

The diagnosis of PAD was confirmed at enrollment by an ABI <0.9 in at least one leg. [17] ABI was calculated from Doppler-derived systolic pressure measurements of the brachial and ankle arteries. The measurement was performed with the patient in a supine position after 10 minutes of rest, using a Doppler ultrasound transducer and a standard blood pressure cuff. [17] Blood pressure was measured and recorded at the posterior tibial arteries (PTA) and dorsalis pedis arteries (DPA) of both limbs. Systolic and diastolic blood pressure in both arms was also assessed.

The arterial pulse was detected twice in the DPA and PTA. ABI was defined as the ratio of the higher systolic blood pressure in the ankle (from either the DPA or PTA) to the higher of the two brachial systolic blood pressure readings. [21]

If patients had claudication and ABI differed between limbs, the limb with the lower ABI was selected for analysis. A duplex ultrasound was also performed to define sites of stenosis or occlusion.

To avoid bias, the ABI was evaluated by two independent operators who were blinded to the patients' clinical data.

2. Functional evaluation

The 6-minute walk test (6MWT) was conducted at baseline and after the 6-month follow-up visit in the same 20-meter corridor. [17, 18] Patients were instructed to walk as far and as rapidly as possible for 6 minutes, with the option to rest and restart if unable to continue walking due to claudication. [22] The following parameters were evaluated:

The pain-free walking distance (PFWD).

The total distance covered (6-minute walking distance [6MWD]).

Total gait speed (m/s).

After enrollment, all patients participated in a supervised exercise program consisting of interval training (walk-rest-walk) performed until moderate to maximum claudication. Each session lasted 30 to 45 minutes, with 3 sessions per week. [23]

Statistical Analysis

The sample size was determined using G*Power software (version 3.1.9.4; Franz Faul, University of Kiel, Germany). The statistical power calculation anticipated a power of 0.85, with an α error probability of 0.05 and a medium effect size for the variables compared.

Baseline characteristics were compared between the two groups. The Kolmogorov-Smirnov test was utilized to assess the normality of variable distributions. Data were presented as medians with interquartile ranges or as means with standard deviations, and categorical variables were presented as proportions. Continuous variables with normal distributions were compared using the Student *t*-test, while those with non-normal distributions were assessed using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test.

The Levene test of equality of error variances was used to assess the homogeneity of data regarding outcomes at 6 months of follow-up. When homogeneity was confirmed, analysis of covariance (ANCOVA) with parameter estimates was conducted to compare changes between groups, using the baseline measure as a covariate. Partial η^2 was employed to assess effect sizes between groups, with values of 0.01 to >0.06 considered small, >0.06 to >0.14 medium, and ≥0.14 large.

All analyses were performed with 95% confidence intervals (CIs), and a *P*-value <0.05 was considered statistically significant. Data analysis was conducted using IBM SPSS Statistics, version 21.0.0 (IBM Corp).

RESULTS

In this prospective cohort study, after applying all exclusion criteria, we included 93 patients in Group I (TMZ group) and 95 in Group II

(control group). We found no significant differences between the two groups regarding all baseline characteristics. The only exception was that all patients in Group I had evidence of CCS, compared with only 34.7% in Group II, which was inherent to our study design (Table 1).

As shown in Table 1, the baseline EF, ABI, and findings from 6MWT were not significantly different between the two groups.

Table 1. Comparisons between the studied groups regarding baseline characteristics

		Group I (n =93)	Group II (n =95)	t/X^2/Z	*P*
Age (y)		56.08±5.27	54.69±5.16	1.814*	0.071
BMI		30.49±3.21	29.82±3.33	1.405*	0.162
Males (%)		59 (63.44%)	62 (65.26%)	0.068$	0.794
Smokers (%)		37 (39.78%)	40 (42.11%)	0.105$	0.746
Smoking Load (packs/y)		90 (240)	90 (180)	-0.472#	0.637
Diabetes	Diabetes Duration (y)	11 (5)	10 (5)	-1.736#	0.082
	Oral Hypoglycemic Drugs (%)	53 (56.99%)	61 (64.21%)	1.027$	0.311
	Insulin (%)	49 (52.69%)	38 (40%)	3.043$	0.081
	HbA1C%	7.3 (1.05)	7.3 (1)	-0.811#	0.418
Macrovascular Diseases	Hypertension (%)	43 (46.23%)	41 (43.16%)	0.180$	0.671
	Cerebrovascular Disease (%)	10 (10.8%)	11 (11.6%)	0.032$	0.857
	Coronary Artery Disease (%)	93 (100%)	33 (34.7%)	90.560$	<0.001**
	Coronary Artery Intervention (%)	18 (19.4%	20 (21.1%)	0.084$	0.772
	PAD Intervention (%)	6 (6.5%)	6 (6.3%)	0.001$	0.970
	History of MI (%)	4 (4.3%)	5 (5.3%)	0.095$	0.757
	B-Blockers (%)	40 (43.01%)	39 (41.05%)	0.074$	0.786
	Calcium Channel Blockers (%)	23 (24.73%)	20 (21.05%)	0.360$	0.548
	ACEI/ARB (%)	39 (41.94%)	36 (37.89%)	0.320$	0.572
	Diuretics (%)	35 (37.63%)	33 (34.73%)	0.171$	0.679
	Aspirin (%)	84 (90.3%)	79 (83.2%)	2.092$	0.148
	P2Y12 inhibitors (%)	53 (57%)	54 (56.8%)	0.001$	0.984
	Prostanoids (%)	6 (6.5%)	8 (8.4%)	0.264$	0.607
	Cilostazol (%)	55 (59.1%)	57 (60%)	0.014$	0.904
	Pentoxifylline (%)	48 (51.6%)	48 (50.5%)	0.022$	0.882
	Total Cholesterol (mg/dL)	210.22±47.24	216.87±43.55	-1.005*	0.316
	LDL-Cholesterol (mg/dL)	131.51±40.08	139.18±41.03	-1.297*	0.196
	HDL-Cholesterol (mg/dL)	44.82±7.89	43.74±7.90	0.938*	0.349
	Triglycerides (mg/dL)	148.23±42.17	149.02±40.86	-0.131*	0.896
Diabetic Kidney Disease	Diabetic Kidney Disease (%)	12 (12.90%)	19 (20%)	1.719$	0.190
	eGFR Stage - 1(%)	21 (22.58%)	24 (25.26%)	0.431$	0.934
	eGFR Stage - 2 (%)	37 (38.78%)	38 (40%)		
	eGFR Stage - 3a (%)	25 (26.88%)	22 (23.16%)		
	eGFR Stage - 3b (%)	10 (10.75%)	11 (11.58%)		
	eGFR (mL/min/1.73m^2)	71.17±24.57	73.29±23.79	-0.602*	0.548
	Albuminuria Stage - A1 (%)	65 (69.89%)	73 (76.84%)	1.163$	0.281
	Albuminuria Stage - A2 (%)	28 (30.10%)	22 (23.16%)		
	Creatinine (mg/dL)	1.16±0.37	1.14±0.34	0.471*	0.638
	UACR	24 (20)	24 (13)	-0.447#	0.655

*: independent sample *t*-test (t)

PAD: peripheral arterial disease, MI: myocardial Infarction, eGFR: estimated glomerular filtration rate, UACR: urinary albumin creatinine ratio

#: Mann-Whitney U test (Z)

$: Chi-square test ($X^2$)

After 6 months, 6-MWT findings-including PFWD, total walking distance, and gait speed-as well as ABI improved significantly in both groups. *P*-values were <0.001 for all parameters in Group I and 0.049, 0.044, 0.043, and 0.011, respectively, in Group II (Table 2).

At the same time, after 6 months of follow-up, Group I (TMZ) demonstrated a statistically significant improvement compared with Group II (control) in the functional parameters of 6-MWT (PFWD, total walking distance, and gait speed), with *P*-values of 0.045, 0.023, and 0.023, respectively. Nevertheless, the groups did not differ significantly with respect to ABI (Table 3).

Table 2. Comparisons between baseline and follow-up 6-WMT, ABI, and EF results

	Baseline (n =93)	Follow-up (n =93)	t/Z	*P*
Group I				
Pain-Free Waking Distance (m)	281.03±26.23	295.42±18.40	-4.330*	<0.001**
Total Distance (m)	293.02±24.18	307.66±21.57	-4.356*	<0.001**
Gate Speed	0.81±0.07	0.85±0.06	-4.356*	<0.001**
ABI	0.8 (0.15)	0.8 (0.20)	-3.197*	0.001**
EF	55.28±5.82	55.29±5.56	-0.013$	0.990
Group II				
Pain-Free Distance (m)	283.14±23.26	289.56±21.28	-1.982$	0.049*
Distance (m)	294.48±22.59	300.74±19.77	-2.030$	0.044*
Gate Speed	0.82±0.06	0.84±0.06	-2.034$	0.043*
ABI	0.80 (0.10)	0.80 (0.20)	-2.553*	0.011*
EF	55.51±5.53	55.49±5.74	0.038$	0.970

6MWT: six-minute walk test, ABI: ankle-brachial index

*: independent sample *t*-test (t)
$: Chi-square test ($X^2$)

Table 3. Comparisons between the studied groups regarding baseline and follow-up 6-MWT, ABI, and EF

	Group I (n=93)	Group II (n=95)	t/X^2/Z	*P*
Baseline				
Pain-Free Distance (m)	281.03±26.23	283.14±23.26	-0.585*	0.559
Distance (m)	293.02±24.18	294.48±22.59	-0.429*	0.669
Gate Speed	0.81±0.07	0.82±0.06	-0.429*	0.669
ABI	0.8 (0.15)	0.80 (0.10)	-0.510#	0.610
Ejection fraction	55.28±5.82	55.53±5.83	-0.290*	0.772
Follow-up				
Pain-Free Distance (m)	295.42±18.40	289.56±21.28	2.018*	0.045*
Distance (m)	307.66±21.57	300.74±19.77	2.294*	0.023*
Gate Speed	0.85±0.06	0.84±0.06	2.285*	0.023*
ABI	0.8 (0.20)	0.8 (0.20)	-0.257#	0.797
New Incident of Diabetic Foot (%)	8 (8.6%)	12 (12.6%)	0.803$	0.370
EF	55.29±5.56	55.49±5.74	-0.248*	0.804

6MWT: six-minute walk test, ABI: ankle-brachial index, EF: ejection fraction

*: independent sample T-test (t)
#: Mann-Whitney U test (Z)
$: chi-Square text ($X^2$)

During the follow-up period, patients in Group I had a lower incidence of diabetic foot requiring amputation (8.6%) than Group II (12.6%); still, the difference was not statistically significant (*P* =0.370) (Table 3).
ANCOVA was used to confirm changes in both groups over time. After the 6-month follow-up, Group I showed statistically significant improvement in 6-MWT results-including PFWD, total walking distance, and gait speed-compared with Group II (F =4.036, 5.238, and 5.172; *P* =0.046, *P* =0.023, and *P* =0.024, respectively). In contrast, ABI did not differ significantly between the groups. Effect sizes favored Group I, with small to medium effects observed for PFWD (η^2 =0.021), total walking distance (η^2 =0.028), and gait speed (η^2 = 0.027) (Table 4).

Table 4. Comparisons of 6MWT results and ABI changes before and after the 24-week follow-up in the studied groups using ANCOVA

6-MWT Results	Group	F	ANCOVA		Effect Size (G I vs G II)
			B (95% CI)	*P*	
Pain-Free Distance	G I	4.036	5.855 (0.105-11.605)	0.046	0.021*
	G II				
Distance	G I	5.238	6.925 (0.955-12.895)	0.023	0.028*
	G II				
Gate Speed	G I	5.172	0.019 (0.003-0.036)	0.024	0.027*
	G II				
ABI	G I	0.148	0.005 (-0.019-0.029)	0.701	0.001
	G II				

6MWT: six-minute walk test, ABI: ankle-brachial index

*: small to medium effect
B: unstandardized coefficients, G: Group

DISCUSSION

PAD is a local manifestation of systemic arterial occlusive disease in the lower extremities. PAD can reduce patients' functional capacity and negatively affect their quality of life. [17] TMZ is commonly used in patients with CCS, and its mechanism of action in ischemic heart disease (IHD) is well understood. [19] Several previous studies suggest that TMZ may help alleviate symptoms and improve exercise capacity in patients with PAD; however, the mechanisms by which the drug exerts these effects remain unclear. Notably, none of these studies focused on the role of TMZ in the subgroup of patients with PAD who have diabetes.
In this study, we aimed to assess the impact of TMZ in patients with diabetes who experienced intermittent claudication as a manifestation of PAD. We also utilized 6-MWT to evaluate patients' functional capacity and utilized ABI to assess hemodynamics in the lower limbs.
The main findings were that patients in both groups demonstrated improvements in exercise capacity and ABI at the 6-month follow-up. Nonetheless, patients in the TMZ group showed greater improvement in exercise capacity compared with those in the non-TMZ group, whereas ABI did not differ significantly between the groups.
These findings indicate that TMZ does not reduce the degree of arterial occlusion, as ABI reflects the extent of arterial narrowing. [24] This suggests that TMZ does not directly affect the pathophysiology of plaque formation, but it may act by modulating myocyte metabolism, thereby improving the cells' tolerance and adaptation to ischemia.

Reduced blood flow and oxygenation distal to arterial narrowing promote anaerobic metabolism, leading to lactic acid accumulation. In addition, increased growth factors and inflammatory cytokines contribute to pain stimulation. [14]

TMZ's mechanism of action involves optimizing aerobic metabolism in skeletal muscles, leading to a reduced need for oxygen to produce ATP molecules. [25] This could result in decreased accumulation of lactic acid and proinflammatory cytokines, ultimately reducing pain. [14] With improved pain management, patients receiving TMZ may be able to walk longer distances. In support of this, Taylor et al. [26] discovered a positive correlation between increased ATP production in skeletal muscle mitochondria and muscle activity levels during treadmill exercise, as well as the walking distance of individuals with PAD.

A study further supporting the potential benefits of TMZ on skeletal muscle activity involved fifty-eight patients with stable angina, who were randomized into a TMZ group or a control group. The researchers observed a significant improvement in 6MWT distance, as well as other parameters of muscle function, such as muscle strength (handgrip and pinch strength), gait speed, muscle endurance, and balance maintenance in the TMZ group compared with the control group after three months of follow-up. [27]

In a study conducted by Chu et al., [28] 72 patients with PAD were examined, with 37 patients receiving TMZ and 35 serving as controls. The authors found that MWD, pain onset time, and maximum walking time significantly improved in the TMZ group compared with the control group.

Vitale et al. [29] reported similar findings in their study, which included one hundred patients with claudication who were randomized to receive TMZ or a matching placebo alongside an exercise program. At the study's conclusion, MWD improved in all patients, but a more notable improvement in MWD was seen in those receiving TMZ.

While the previously discussed studies were randomized, double-blinded trials, our study differed in design. Our study included a larger sample size and a longer follow-up period than the aforementioned studies. Intriguingly, the potential benefits of TMZ in PAD have also been investigated in animal models. In a study by Yang et al., [30] diabetic mice underwent femoral artery ligation to induce lower extremity ischemia, followed by 2 weeks of TMZ treatment. The researchers assessed various markers of ischemic damage, such as hindlimb ischemia, function, capillary density, vascular endothelial growth factor (VEGF) expression, myogenic regulators, and serum intercellular adhesion molecule 1 (ICAM-1) levels. Mice treated with TMZ demonstrated milder ischemic impairment, with partially reversed reductions in capillary density in the gastrocnemius muscles of the ischemic hindlimb, VEGF expression, myogenic markers, and serum ICAM-1 levels.

Several studies have also explored the comparative effectiveness of TMZ with other drugs in treating PAD. Yong et al., [31] for instance, compared TMZ with plasmin combined with alprostadil in a study involving 132 patients with PAD, who were followed for one month. They discovered that MWD was significantly greater in the TMZ group than in the plasmin group. Interestingly, their findings on pain-free walking distance did not show a statistically significant difference between the groups, unlike the results of our study.

In terms of ABI, various studies have reported no significant influence of TMZ on ABI, which chimes with our observations. [29, 30]

Conversely, a study by Hu et al. [32] compared TMZ with cilostazol and found a significant improvement in the toe-brachial index in both groups after treatment. Nevertheless,

the improvement was more pronounced in the cilostazol group compared with the TMZ group.

In our study, we also analyzed the incidence of diabetic foot requiring amputation between the TMZ and control groups during the 6-month follow-up period. We observed an 8.6% incidence in the TMZ group and a 12.6% incidence in the control group. Although the incidence was lower in the TMZ group, the difference was not statistically significant. The nonsignificant difference in diabetic foot amputation incidence between the groups may be attributed to their similar baseline diabetic profile characteristics. Moreover, TMZ's primary mechanism is likely related to improving skeletal muscle metabolism rather than directly affecting plaque formation or the degree of arterial stenosis. Thus, it is reasonable to assume that TMZ may not considerably impact limb hemodynamics and ischemic changes due to reduced blood flow. This particular aspect has not been previously studied, indicating that further research is warranted to elucidate TMZ's potential effects on lower extremity ischemia, particularly in diabetic patients.

Our study encountered several limitations. Firstly, it was a non-randomized study with a relatively small sample size. Additionally, there was a notable variation in the prevalence of IHD between the TMZ group, where all patients had evidence of IHD, and the control group, where only one-third of patients had IHD. To minimize the impact of this discrepancy, we excluded patients with ACS or those whose exercise capacity could be affected by chest pain, as these factors could potentially influence 6MWD.

CONCLUSIONS

Our study, therefore, indicated that adding TMZ to GDMT and exercise programs may improve walking performance in diabetic patients with symptomatic PAD. Furthermore, the addition of TMZ may reduce the rate of diabetic foot amputation, offering a potential therapeutic strategy for managing these conditions.

Declarations

Ethics Approval and Consent to Participate:

The study protocol was conducted in accordance with the Declaration of Helsinki. The Beni-Suef University Committee of Research and Medical Ethics (approval No. FMBSUREC/06122022/Amin) in December 2022 and the Tanta University Committee of Research and Medical Ethics (code 36053/11/22) in November 2022 both approved the study protocol. To ensure patient autonomy and respect, we obtained written informed consent from all patients.

Consent for Publication:

Not applicable.

Availability of Data and Materials:

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors declare no competing interests.

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Clinical Trial Number:

Not applicable.

Authors' Contributions:

O.A. enrolled the patients, performed noninvasive tests, and wrote the manuscript. M.A. followed the patients and contributed to writing the manuscript. A.H. analyzed and interpreted the data and contributed to writing the manuscript. A.A. enrolled the patients, performed follow-up, and revised

the manuscript. All authors read and approved the final manuscript.

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