SYSTEMATIC REVIEW

Revisiting the role of trimetazidine for peripheral artery disease: a systematic review with meta-analysis

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Abstract

Objective: To examine the impact of trimetazidine on skeletal muscle function in patients suffering from peripheral artery disease.

Method: The systematic review was conducted from July 20 to November 22, 2022, in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis and comprised search for interventional studies on MEDLINE, ProQuest, Scopus and ScienceDirect databases using key words "peripheral artery disease" and "trimetazidine" or their synonyms. The cut-off date for the search was July 21, 2022. Clinical parameters, including Ankle-Brachial Index, Maximum Walking Distance, Maximum Walking Time and Pain Onset Time, were analysed both narratively and quantitatively whenever possible.

Results: Of the 587 studies initially identified, 12(2%) were shortlisted. Of them, 2(16.7%) qualified for detailed analysis, comprising 172 patients with intermittent claudication. There was no significant difference between the examined groups' Ankle-Brachial Index values at baseline and post-intervention (p=0.83). Maximum Walking Distance improvement was significantly higher (p=0.0006) in trimetazidine group compared to control group. Maximum Walking Time MWT and Pain Onset Time were significantly different between control and trimetazidine groups (p<0.05).

Conclusion: Trimetazidine's anti-ischaemic effect in peripheral artery disease patients improved Maximum Walking Distance, while it had no significant influence on Ankle-Brachial Index. Well-designed studies addressing the issue are needed.

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Introduction

Peripheral arterial disease (PAD), a circulatory issue, causes less blood to flow in the arteries of lower extremities[1]. PAD affects more than 200 million adults globally[2], and its prevalence continues to rise[3]. Surprisingly, the trend shows higher incidence (7.4%) in high-income countries (HICs) than the rest of the world (5.1%). However, considering the population size, the majority of those with PAD (72.9%) live in in low- and middle-income countries (LMICs)[4].

Narrowed arterial lumen causes oxygen supply-demand mismatch, which manifests as pain, cramps or fatigue that eventually causes the patients to slow down or stop walking[5, 6]. The symptoms vary according to the disease stage[7]. Ankle-Brachial pressure Index (ABI) is a simple and valuable examination that reflects distal perfusion of the lower extremity, which is the hallmark PAD[8]. However, PAD is often unrecognised and undiagnosed, and is usually linked to decreased life quality, mobility limitation and amputation[9]. In addition, the critical risk of systemic atherothrombotic incidents, such as stroke, cardiovascular mortality, and myocardial infarction (MI), is also frequently linked to peripheral arteries[9].

Anti-ischaemic drug trimetazidine (TMZ) is frequently used to treat stable coronary artery disease (CAD) and chronic heart failure (CHF). This medication prevents cardiac fatty acid intake, which stimulates glucose oxidation and increases mitochondrial metabolism by inhibiting the long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT) enzyme in mitochondria[10, 11]. It works indirectly by optimising glucose oxidation (aerobic metabolism), which decreases the amount of lactic acid build-up, proinflammatory cytokines, and other pain mediators associated with ischaemic injury, leading to improvement in symptoms[12]. Previous studies examined the possible use of TMZ for those suffering from atherosclerotic lesions in the peripheral arteries[13].

However, the role of TMZ in PAD is unclear. Therefore, the current systematic review was planned to evaluate the current evidence of TMZ's effect on PAD patients, especially in patients with intermittent claudication.

Materials and Methods

The systematic review was conducted from July 20 to November 22, 2022, in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [14], and comprised search for interventional studies on MEDLINE, ProQuest, Scopus and ScienceDirect databases using key words "peripheral artery disease" and "trimetazidine" or their synonyms. The cut-off date for the search was July 21, 2022. The review and its detailed protocol were registered with the International Prospective Register of Systematic Reviews (PROSPERO) https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022350422)

The search was conducted independently by 3 investigators. Any disagreement was resolved by an independent researcher. The literature was restricted to studies published in the English language, and any titles or abstracts considered admissible for inclusion were acquired for full-text evaluation.

Studies that met the following requirements were considered for this review: any trials/observational studies investigating the administration of TMZ in PAD; any trials/observational studies where the participants were aged >16 years regardless of gender who were diagnosed with intermittent claudication PAD (Fontaine/Rutherford Class IIa-IIb/1-3)[15]. The current review involved studies discussing the management of any TMZ form, route or dosage, as well as placebo or standard of care as the comparing parameter regarding the type of intervention.

Data was extracted from each study, including author and year of publication, patients' characteristics, like age range and gender, studies' characteristics, like design, population, sample size, intervention, comparison, treatment duration and standard of care, as well as the outcomes, including ABI, Maximum Walking Distance (MWD), Maximum Walking Time (MWT) and Pain Onset Time (POT).

The methodological quality of the studies was evaluated using the Cochrane Risk of Bias tools version 2 for randomised trials, Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) and the Newcastle Ottawa Scale (NOS) for observational studies[16, 17]. Data extraction and bias assessment were done independently by 3 investigators. Any disagreement was resolved by an independent researcher.

A narrative synthesis of the pooled studies' findings was done. Whether or not to conduct quantitative synthesis depended on the number of studies and the feasibility of combining the outcomes. Categorical data of clinical outcomes was estimated by the summary of pooled relative risks (RRs) or odds ratios (ORs) and their appropriate 95% confidence interval (CI), while continuous outcome were estimated by the summary of pooled (standardised) mean differences. The overall effect was assessed using the Z-test, and $p<0.05$ was considered significant. Heterogeneity was appraised through Q-statistic test and I^2 test. The pooled estimated RRs or ORs were measured with models based on fixed effects or random effects assumptions. In case of $p>0.1$ or I^2 value <50%, the fixed-effects model was applied, otherwise, the random-effects model was applied. Begg's funnel plot and Egger's test were used to determine publication bias (Higgins JPT et al., 2011). Forest plots were generated using Review Manager version 5.4 (Cochrane Collaboration, London, United Kingdom).

Results

Of the 587 studies initially identified, 12(2%) were shortlisted. Of them, 2(16.7%) qualified for detailed analysis (Figure 1), comprising 172 patients with intermittent claudication[18, 19]. Vitale et al. was assessed to have high risk due to heterogeneity in the baseline MWD between the groups. Also, the results for each group showed an increase compared to the baseline, which was not expected in the study design[19](Figure 2A). Chu et al. was assessed to have low risk of bias for all domains[18] and was a well-performed randomised trial (Figure 2B).

Chu et al. study had a total of 72 PAD patients consecutively recruited as per the inclusion criteria which entailed ABI index <0.9, colour Doppler flow imaging of peripheral blood vessel confirmed the reduction in the diameter of the femoral artery, tibial artery and dorsal artery of the foot, the intimate was thickened, atherosclerotic plaque formation could be seen, decreased blood flow velocity, and Rutherford classification grade 2-3 [18]. The study showed that gender distribution, age, hypertension, smoking, diabetes, drug consumption and coronary heart disease values were significantly different at baseline, resulting in careful interpretation. The patients' blood pressure, body mass index (BMI), lipid profile, and glycaemia status were homogenous at baseline.

Vitale et al[19]. study had 100 outpatients with a diagnosis of PAD based on ABI <0.90, and vascular stenosis was observed on ultrasound or radiological examination in at

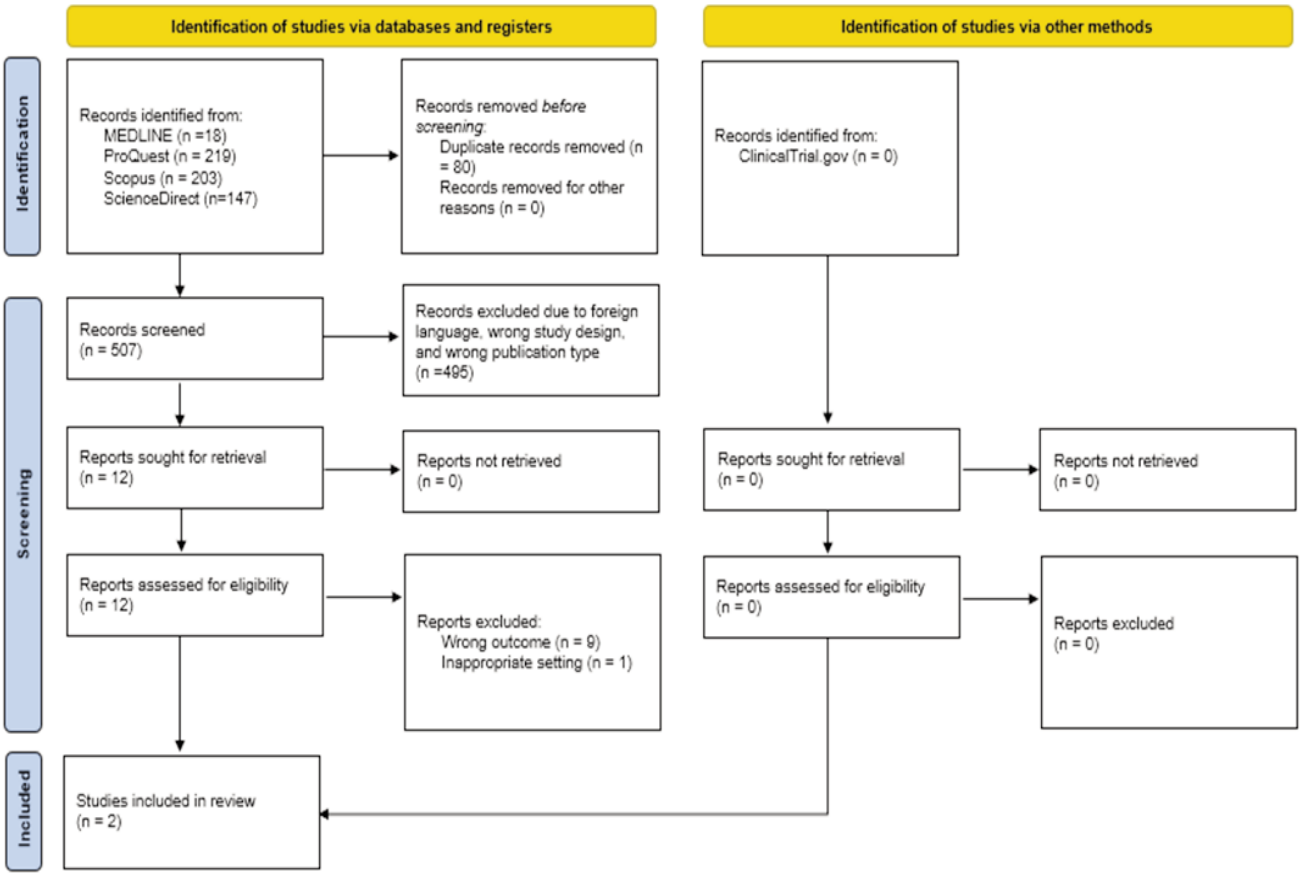

Figure-1: Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow-chart.

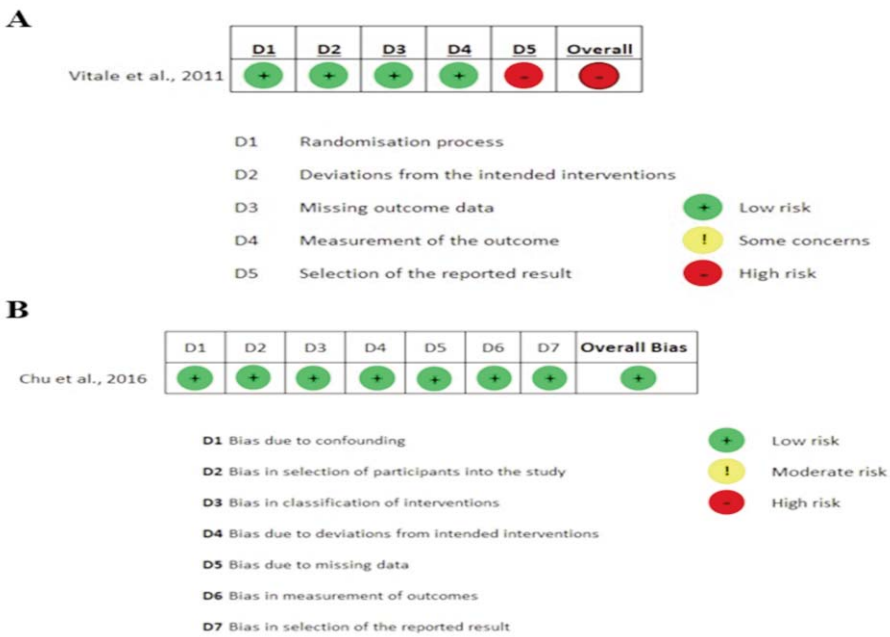

Figure-2: Risk of bias assessment randomised controlled trial (RCT) (A) and non-randomised control trial (B).

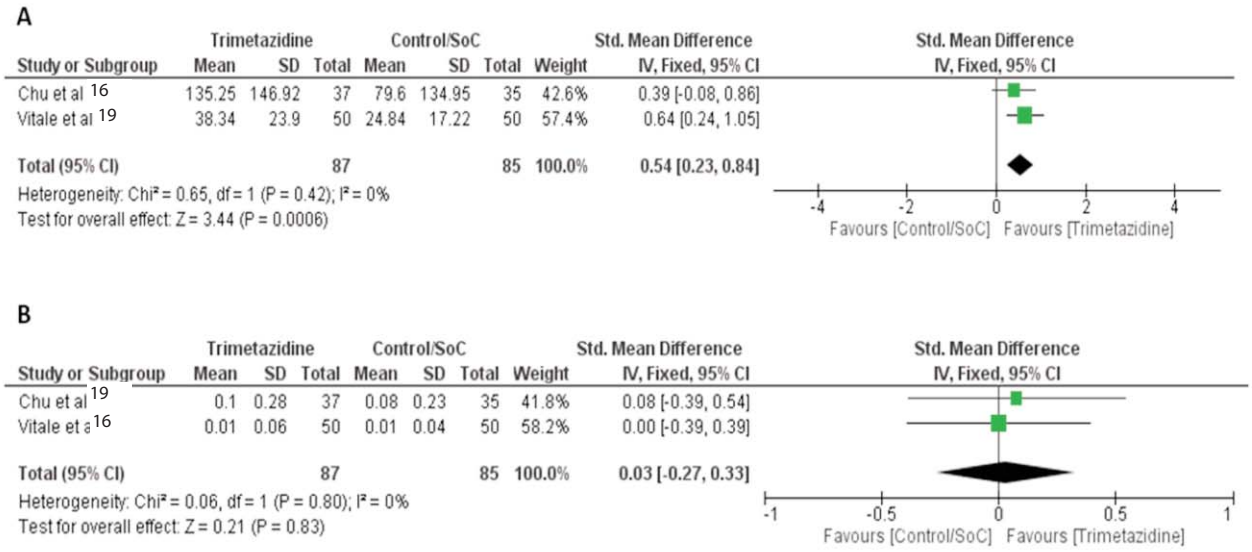

Figure-3: Forest plot showing Maximal Walking Distance (MWD) improvement comparison between trimetazidine and control groups (A) and Ankle-Brachial Index (ABI) improvement comparison between the groups (B).

least one leg vessel, and functionally was damaged owing to claudication while receiving optimal medical therapy and intermittent claudication with Pain-Free Walking Distance (PFWD) 100m <x(m) <400m, without any evidence of resting pain, foot ulcer, critical limb ischaemia, and serious amputation, without history/planned major surgery (within 3 months), without orthopaedic and neurological problems which could affect poorly-controlled hypertension, walking ability, unstable coronary artery and/or severe valvular disease, chronic obstructive pulmonary disorder (COPD) and dementia[19]. The sample was statistically determined as homogenous for age, BMI, blood pressure, lipid profile, glycaemia status, and ejection fraction at baseline[19].

In the study by Chu et al.,[17] the participants were divided into 2 treatment groups according to patients' preference. In the control group, the participants were given conventional treatment, including aspirin 100mg/d, statins (mainly rosuvastatin calcium) 10mg/d, and antihypertensive drugs. The intervention group received conventional treatment plus TMZ hydrochloride tablets 20mg three times a day (TDS)[18]. All the participants were instructed lifestyle modification and exercises for about 2 weeks.

In the study by Vitale et al., the patients were enrolled in a parallel, double-blind, three-month study[19]. The patients randomly received TMZ or a corresponding placebo, and both groups participated in a domiciliary exercise programme. In the intervention group, 50 patients were treated with TMZ 20mg TDS, while in the control group, 50 patients received a matching placebo[19]. Domiciliary exercise programme included one-hour daily training sessions at least 5 days a week for 3 months (Vitale et al., 2011).

As for the outcomes, ABI and MWD were reported by both the studies, while Chu et al. also reported MWT and POT [18, 19]. Vitale et al. assessed ABI and MWD before and after three months of intervention. ABI was similar at baseline in both groups, and neither group appeared to have changed significantly by the end of the study (0.83±0.04 vs. 0.85±0.03, TMZ vs. placebo, respectively). Due to significant differences in MWD of both groups at baseline, they presented the MWD as a relative increase to baseline for each group. They found that patients in the TMZ arm exhibited a significantly higher percentage of improvement concerning each baseline than in the placebo-receiving arm at 1 month (10% [95% CI: 9-11%] vs. 7% [95% CI: 6-8%]; p<0.001; TMZ vs. placebo, respectively) and at the end of the study period (23% [95% CI: 22-24%] vs. 14% [95% CI: 13-15%]; p<0.001, TMZ vs. placebo, respectively)[19].

Regarding MWD, Chu et al. also demonstrated a significant improvement of MWD before and after the study period though their study frame was longer (6 months) than Vitale et al. (3 months). Additionally, they also showed a significant improvement of ABI in both arms after 6 months, while Vitale et al. reported no significant improvement over 3 months[18,19]. Notwithstanding, the improvement of ABI between the investigated groups was not significantly different

(p>0.05). That study also reported similar improvement in MWD, MWT and POT at the end of the study compared to the baseline. Interestingly, Chu et al. demonstrated that MWD (245.74±118.57 vs. 192.22±105.44, p<0.05), MWT (15.85±2.98 vs 12.11±3.08, p<0.05), and POT (9.43±1.81 vs. 7.43±1.72, p<0.05) improvements were significantly better in TMZ group compared to the control group (p<0.05).[17]

A quantitative comparison could only be done for ABI and MWD in 172 patients between intervention and control arms of the 2 studies[18, 19]. This was done on the basis of mean increase post-intervention.

MWD was significantly higher in the TMZ arm compared to the controlled arm (Standardized Mean Difference (SMD)=0.54 [0.23, 0.84], p=0.0006, I2=0%, fixed effect) (Figure 3A). However, pooled findings on ABI showed no significant difference (SMD=0.03 [-0.27, 0.33], p=0.83, I2=0%, fixed-effect) (Figure 3B).

Discussion

PAD is a condition in which the arteries are narrowed outside the heart, specifically the ones in the lower extremities, reducing blood flow in the peripheral artery[1, 2]. Most PDA is asymptomatic, but if it continues untreated, the muscles get starved of oxygen, and claudication appears[2]. Recently, TMZ, an anti-ischaemic agent, has been introduced for PAD patients[20]. To our knowledge, the current meta-analysis and systematic review is the first such attempt to address the issue.

TMZ is a cytoprotective medication that, through several mechanisms of action, normalises metabolic abnormalities in low-flow ischaemia. The most well-known way TMZ works is by preventing the oxidation of free fatty acids (FFAs)[20]. TMZ accelerates the metabolism of glucose by specifically blocking LC 3-KAT, the FFA-oxidation pathway's last enzyme[20, 21]. Additionally, TMZ improves the activity of the enzyme pyruvate dehydrogenase, which reduces the amount of oxygen used during the synthesis of adenosine 5′-triphosphate (ATP), creating hydrogen ions, intracellular acidosis, and reduced accumulation of calcium ions[20]. Another aspect of TMZ mechanism that may be crucial for people with cardiovascular disease, including those who have CHF, is its direct suppression of cardiac fibrosis through enhancing connective tissue growth factor (CTGF)[20]

ABI is a simple, feasible, non-invasive and affordable test tool for diagnosing PAD[22]. According to the American Heart Association (AHA), PAD is diagnosed when ABI is ≤0.9[23]. As ABI reflects the degree of arterial occlusion due to lumen narrowing, it could be used as one of the therapeutic parameters in PAD[24]. The 2-studies currently reviewed individually showed that ABI improvement between TMZ-receiving and control arms at the end of the study were not markedly different. It was confirmed by the pooled finding, which also found non-significant differences in SMD between the groups. This finding could have been because TMZ did not work on the pathogenesis and pathophysiology of plaque formation. However, this conclusion should be considered an interim finding in the setting of the scarcity of evidence as the therapy evaluation was considered for short periods of 3 and 6 months.

Progressive deterioration of the arterial lesion causes claudication and reduces walking capacity. Clinical evidence of a decline in walking ability at POT and MWD supported this theory. This test is often done until the pain becomes more severe at a steady pace and flat surface. According to the Fontaine or Rutherford classification, MWD is the major index for determining the severity of PAD[25].

The current pooled findings suggested that the MWD improvement was notably higher in TMZ group than in the control group (p<0.001) (Figure 3A). This finding was in line with literature regarding TMZ administration in patients with intermittent claudication. Reduced blood flow and oxygenation distal to the lumen narrowing promotes cellular anaerobic metabolism, leading to the lactic acid build-up in the interstitium. Growth factors and inflammatory cytokines release are also increased as the muscle tissue is hypoxic. The build-up of anaerobic metabolites and endogenous substances lead to various receptors and channels of upregulation involved in sensory input transmission and are perceived as pain stimuli by the central nervous system (CNS)[12]. According to a prior study, the maximal rate of ATP synthesis in skeletal muscle mitochondria was positively correlated with the activity level of the muscle during treadmill activity, and the walking distance of those with PAD was inversely related to their adenosine diphosphate (ADP) concentration[26]. TMZ works by optimising aerobic metabolism in skeletal muscle and reducing the amount of oxygen needed to produce ATP[20]. This can lead to delay in the accumulation of lactic acid, proton, proinflammatory cytokines and growth factors that could stimulate pain in peripheral nerve-ending[12]. The patients eventually can perform longer walking distances as the pain improves. This possible explanation could also explain better MWT and POT in TMZ group compared to the control group[18].

The current review has several limitations. The number of pooled data was considerably low (n=172). One of the

included studies did not practise randomisation, and another might have had a selection of reported result issues. Moreover, there was a study with unequal baseline characteristics, calling for careful interpretation of the findings. However, the current review might be a stepping stone for further exploration to enrich data in this field.

Conclusion

Evidence suggested the beneficial role of TMZ in PAD by improving patients' ischaemia-related symptoms through its anti-ischemic mechanism. As the evidence in this field is considerably scarce, further exploration with well-designed studies with larger sample sizes participants is needed.

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