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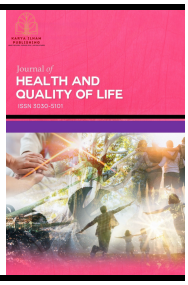
Journal of Health and Quality of Life

Journal homepage:
https://karyailham.com.my/index.php/jhqol/index
ISSN: 3030-5101



Peripheral Arterial Disease in Diabetes Mellitus and Physiotherapy Management: A Narrative Review

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ARTICLE INFO

Article history:
Received 13 October 2024
Received in revised form 1 November 2024
Accepted 20 November 2024
Available online 15 December 2024

Keywords:
Peripheral arterial disease; diabetes mellitus; physiotherapy management

ABSTRACT

Diabetes Mellitus is prevalent and contributed to high mortality rate. The hyperglycemia in diabetic individual leads to low-grade inflammation, vasoconstriction, arterial stiffness, endothelial dysfunction and thrombotic abnormalities. These placing them at higher risk of developing peripheral arterial disease which compromised the blood perfusion, particularly the lower extremity. Despite the development of peripheral arterial disease in Diabetes Mellitus can leads to wide array of complications and leaves the individual with great disability, however, various physiotherapy interventions have been supported by previous literature to be able to improve the functional outcomes and quality of life. This first part of this review paper focused on the pathophysiology of peripheral arterial disease in Diabetes Mellitus, while the second part focused on the various physiotherapy interventions for improving the functions and outcomes in diabetic individual with peripheral arterial disease.

1. Introduction

According to the International Diabetes Federation, diabetes is affecting approximately 635 million people worldwide and has contributed to more than 6 million deaths in 2021. Although the disease incidence has begun to decline in some nations, diabetes prevalence has climbed over the past few decades in the majority of other developed and developing nations especially the Southeast Asian Countries. South-East Asia is among the regions with the highest number of people with diabetes, contributing to about 90 million and the figure is projected to escalate to 151 million by 2045. The advances in the management of diabetes mellitus have successfully increased the life expectancies, however, diabetes continues to pose a considerable burden on millions of people living with diabetes mellitus. The global age-standardised disability-adjusted-life-years (DALYs) linked with diabetes in 2019 was 801.5 per 100,000, an increase of nearly 30% when compared to 1990 [32]. The healthcare cost associated with diabetes is tremendous. Globally, it has caused at least USD 966

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https://doi.org/10.37934/jhqol.4.1.1824

billion dollars, more than 300% increase over the last 15 years (International Diabetes Federation, 2021) [15]. In Malaysia, it is estimated that about 20% of its adult population was having diabetes and the estimated total healthcare cost was approximately USD 600 million [10]. Spending on managing diabetes and its complications constitutes one of the direct medical expenses associated with the disease. These expenses cover long-term care, medication, and medical supplies in addition to outpatient, emergency, and inpatient hospital care.

Diabetes mellitus has been known to cause a wide array of complications including peripheral arterial disease. Previous literature suggested that Diabetes Mellitus is associated with greater severity and more diffuse peripheral arterial disease as well as lower extremity complications relative to non-diabetics, which may increase the risk for lower limb amputation four to five times higher [24]. Studies reported that chronic hyperglycemia is often being observed in diabetic individual, which leads to low-grade inflammation, vasoconstriction, arterial stiffness, endothelial dysfunction and thrombotic abnormalities [24,36]. All of which would affect and reduce the blood circulation to the limb, negatively impacting the perfusion to the lower limb. As a result, this would lead to an increased risk for amputation, cardiovascular disease, stroke and risk of death. In fact, Criqui *et al.,* [8] has reported that lower extremity arterial disease often accompanied with intermittent claudication and ulcer and is one of the main risk factors for impaired physical function and reduced physical activity.

2. Peripheral Arterial Disease in Diabetes Mellitus

Peripheral arterial disease is a form of atherosclerotic disease characterised by the occlusion of the blood vessels, compromising the blood perfusion. It is known that Diabetes Mellitus increases the risk of peripheral arterial disease and also accelerates the disease progression and severity. Previous literature has found that people with Diabetes Mellitus are at 2 to 4 times greater risk of developing peripheral arterial disease when compared to their counterpart [4]. The typical presentation of peripheral arterial disease is intermittent claudication, although some may be asymptomatic. Intermittent claudication usually manifested as cramping, numbness or burning sensation at the lower extremity which was brought upon by physical activity and relieved by rest [8]. The most severe form of peripheral arterial disease is chronic limb-threatening ischaemia. Diabetic individuals with chronic limb-threatening ischaemia often complain of diffuse burning or aching pain at the foot and leg, which somewhat improved with dependent positioning of the limb [3]. Tissue loss is a common consequence seen in diabetic individuals with peripheral arterial disease. The compromised blood perfusion at the lower extremity increases the likelihood of ulceration and infection, which eventually would lead to amputation when the tissue damage is irreversible.

In Diabetes Mellitus, the overproduction of advanced glycation end products has long been proposed as the principal mechanism for causing peripheral arterial disease [35,38]. The overproduction of advanced glycation end products (AGEs) could contribute to the development of peripheral arterial disease via 2 main pathologic pathways: 1) abnormal cross-linking of proteins and 2) cellular stress response by interaction with the receptors for advanced glycation end products [9]. Several AGEs, especially pentosidine which formed as a result of non-enzymatic glycation, played a significant role in the development of angiopathic complications in individuals with Diabetes Mellitus [16]. In the study done by Kerkeni *et al.,* [18] which investigated 200 subjects with Diabetes Mellitus, the authors reported that pentosidine level was found to be significantly higher in diabetic subjects and it is positively associated with microvascular complications in Diabetes Mellitus. Pentosidine aggravates the cross-linking formation between and within collagen and elastin proteins which adversely affect the vessel's distensibility and contribute to increased arterial stiffness [34,35].

On the other hand, the AGEs could also lead to excessive cellular stress responses via its engagement with the receptors for advanced glycation end products (RAGE). RAGE is a signal-transducing receptor for AGEs and expressed in various cell membranes including endothelial and smooth muscles [38]. Previous studies have reported there is increased expression of RAGE in people with Diabetes Mellitus [2,30]. The binding of AGEs to RAGE promotes the activation of nuclear factor-kappa B (NF-kB) which up-regulates the release of pro-inflammatory cytokines leading to endothelial dysfunction [9]. As a result, it induces structural as well as functional vascular abnormalities, altering the reactivity and relaxation of blood vessels which stimulate atherosclerosis [24]. Along with the arterial stiffness due to the aggravated cross-linking of proteins, they contribute to the pathogenesis of peripheral arterial disease in diabetic individuals, compromising the blood perfusion to the extremity.

3. Physiotherapy Interventions for Peripheral Arterial Disease

3.1 Resistance Training

A recent randomised controlled trial by Alni and Nikookheslat [1] investigated the effectiveness of resistance training in diabetic individuals with peripheral vascular disease. The resistance training consists of various upper body, lower body and trunk exercises performed at 8-12 repetitions for two to three sets. Significant improvement was noted in the ankle-brachial index after 12 weeks of intervention and the improvement was significantly better when compared to the aerobic exercise group and control group. In Diabetes Mellitus, the overproduction of AGEs lead to dysfunction of endothelial cell as well as smooth muscle in the arteries [24,38]. In addition, the hyperglycemia also causes increased in blood viscosity and platelet aggregation in diabetic individuals which further worsen the blood flow and perfusion [12,23]. The clinical guideline by American Heart Association/American College of Cardiology has recommended the prescription of resistance exercise in patients with Diabetes Mellitus [11]. Resistance training is beneficial in increasing the muscle mass and strength which could help to improve the glucose metabolism [13]. Moreover, previous literature has also reported that exercise is beneficial in improving the concentration of endothelin-1 and nitric oxide which are essential in regulating the arterial function [25,33]. A systematic review and meta-analysis by Liu *et al.,* [20] which included 24 trials comprising more than 900 subjects has also reported that resistance training, particularly when performed at high intensity, has significant effect in decreasing the HbA1c level in diabetic individuals. This could be another plausible reason as to how resistance training could help in improving peripheral arterial disease in people with Diabetes Mellitus as HbA1c has been reported previously that it is significantly associated with vascular complications [31].

3.2 Walking Exercise

In people with Diabetes Mellitus, previous literature has reported the population often exhibit deterioration in their walking performance [19,37]. Declination in muscle strength, sarcopenia, neuropathy and intermittent claudication associated with peripheral artery disease are among the factors affecting their walking performance [5,7,17,29]. In the experimental study by McDermott *et al.,* [21], the authors have investigated the effectiveness of a 6-month supervised treadmill walking on improving walking distance. It was found that supervised treadmill walking did able to significantly improve the walking distance by 6-month follow up, however, the improvement was not maintained when being further followed up at 12-month. Contrary to supervised treadmill, Collins *et al.,* [6] investigated the effects of a home-based walking intervention in diabetic population with peripheral

arterial disease. At 6-month follow up, it was being reported that the walking speed and quality of life demonstrated significant improvement although no significant effect was observed on the subjects' walking distance. Regular walking exercise has been shown that it has positive effects on body weight, muscle strength, blood pressure, skeletal muscle oxygenation as well as glycemic control which could help to improve the walking performance in diabetic individuals with peripheral artery disease [22,27]. The exercise therapy guidelines by American Heart Association has also provided class I recommendation for the prescription of supervised exercise to improve the functional status and leg symptoms in peripheral artery disease individuals with claudication [11].

3.2 Buerger-Allen Exercise

Buerger-Allen exercise is theorised to improve the lower extremity blood circulation, aid in the removal of blood that had become stagnant as well as establishing collateral circulation to the ischemic area. This mechanism is achieved by utilising the effect of gravity and alternatively fills and empties the blood vessel, thus improves the lower limbs circulation of the individual. A study done by Radhika *et al.,* [28] in 2020 evaluated the effect on Buerger-Allen exercise in improving the lower limb perfusion among Diabetes Mellitus population and it has been reported a nearly twofold improvement in the lower limb perfusion as indicated by ankle-brachial index post-intervention. Hafid *et al.,* [14] conducted an experimental study in 2020 to see the effect of Buerger-Allen exercise on Type 2 Diabetes Mellitus population. In this particular study, a significant increase in the ABI value in the peripheral circulation was documented. These outcomes suggest the use of this strategy, Buerger-Allen exercise is effective in improving the lower extremity blood circulation in Diabetes Mellitus population as theorised. Similar outcomes were seen in the study done by Patidar *et al.,* [26] in 2018 as well. Another similar research was done in 2018 by Zahran *et al.,* [39]on 48 adult patients with type 2 Diabetes Mellitus who visited a specialised medical centre for six months. According to the authors, Buerger-Allen exercise was able to significantly improve the lower limb perfusion both immediately post-intervention and even four weeks later when the subjects were being monitored again.

4. Conclusion

Diabetes is amongst the biggest global public health issues, having a significant negative impact on both socioeconomic development and public health globally. The disease, if not managed well, often leading to high disability and substantial healthcare cost. The overproduction of AGEs seen in Diabetes Mellitus causes abnormal cross-linking of proteins and cellular stress response which adversely affecting the structural and functionality of artery, giving rise to peripheral artery disease. Peripheral artery disease characterised by occlusion of the vessel and the most common presentation is intermittent claudication. Previous studies have provided evidences in supporting physiotherapy interventions such as resistance training, walking intervention as well as Buerger-Allen exercise in improving the leg symptoms and function in diabetic individuals with peripheral artery disease.

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