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Review

A systematic review to evaluate the effectiveness of carnitine supplementation in improving walking performance among individuals with intermittent claudication

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ABSTRACT

Objective: To evaluate the evidence for the use of carnitine supplementation in improving walking performance among individuals with intermittent claudication.
Design: Systematic review.
Methods: An electronic search of the literature was performed using MEDLINE (PubMed), Scopus, Cochrane Central Register of Controlled Trials and The Cochrane Library from inception through to November 2012. Search terms included peripheral arterial disease, intermittent claudication and carnitine. Reference lists of review articles and primary studies were also examined. Full reports of published experimental studies including randomized controlled trials and pre-test/post-test trials were selected for inclusion. A quality assessment was undertaken according to the Jadad scale.
Results: A total of 40 articles were retrieved, of which 23 did not meet the inclusion criteria. The 17 included articles reported on a total of 18 experimental studies of carnitine supplementation (5 pre-test/post-test; 8 parallel RCT; 5 cross-over RCT) for improving walking performance in adults with intermittent claudication. For pre-test/post-test studies, 300–2000 mg propionyl-L-carnitine (PLC) was administered orally or intravenously for a maximum of 90 days (7–42 participants) with statistically significant improvements of between 74 m and 157 m in pain free walking distance and between 71 m and 135 m in maximal walking distance across 3 out of 5 studies. Similarly, PLC (600 mg-3000 mg) was administered orally in 7 out of 8 parallel RCTs (22–485 participants), the longest duration being 12 months. All but one of the smallest trials demonstrated statistically significant improvements in walking performance between 31 and 54 m greater than placebo for pain free walking distance and between 9 and 86 m greater than placebo for maximal walking distance. A double-blind parallel RCT of cilostazol plus 2000 mg oral L-carnitine or placebo for 180 days (145 participants) did not demonstrate any significant improvement in walking performance. Of 5 cross-over RCTs (8–20 participants), 4 demonstrated significant improvements in walking performance following administration of 300–6000 mg L-carnitine or PLC. Compared to placebo, pain free walking distance and maximal walking distance improved by 23–132 m and 104 m respectively following carnitine intervention.
Conclusions: Most trials demonstrated a small or modest improvement in walking performance with administration of PLC or L-carnitine. These findings were largely independent of level or quality of evidence, while there was some evidence that intravenous administration was more effective than oral administration and those with severe claudication may achieve greater benefits than those with moderate claudication. Routine carnitine supplementation in the form of PLC may therefore be a useful adjunct therapy for management of intermittent claudication. Further research is warranted to determine the optimal form, duration, dose and safety of carnitine supplementation across the spectrum of peripheral arterial disease severity and its effect with concurrent supervised exercise programs and best medical therapy. These studies should be supplemented with cost effectiveness studies to ensure that the return on the investment is acceptable.

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Contents

1. Introduction

Peripheral arterial disease (PAD) is a major public health problem worldwide. Its prevalence is estimated to be 3–10%, increasing to 15–20% for individuals over 70 years, with risk being greater for smokers and individuals with chronic conditions such as diabetes, hypertension and hyperlipidaemia [1].

Intermittent claudication is the most frequent symptom of mild-moderate PAD and is associated with significant functional impairment [2]. While attempts at revascularisation can be considered for those at the more severe end of the spectrum, conservative management with the aim to slow disease progression and improve functional capacity and pain free walking distance (PFWD) is desirable. This has traditionally consisted of pharmacotherapy and exercise training [3].

Supervised exercise training is the current gold-standard of treatment for intermittent claudication based on recommendations from meta-analyses reported in a Cochrane systematic review [4] and the TASC II consensus guidelines [1], however, the effect of such an intervention is modest at best. Furthermore, compliance with supervised exercise is poor and the physical and economic burden, both to the individual and health care-system, associated with long term exercise interventions is significant. An adjuvant or alternative treatment option therefore remains highly sought-after.

In addition to standard cardiovascular risk-modifying drugs including statins, anti-platelets and anti-hypertensives, many pharmacological agents have been proposed for the treatment of intermittent claudication. Of these, cilostazol is the most widely recognised and meta-analyses have confirmed its beneficial effect on walking performance in claudicants [5]. Like supervised exercise however, this effect is only modest and it is often poorly tolerated due to associated side-effects.

L-Carnitine is a quaternary ammonium compound which can be synthesised endogenously or obtained from diet. Together with two short carnitine esters, it makes up the endogenous carnitine pool [6]. It plays a key role in the transfer of the energy source acyl-coenzyme A (CoA), an intermediate metabolic product of fatty acids and carbohydrates, across the mitochondrial membrane where it is oxidised in the Krebs cycle to produce energy [7,8]. In addition, it acts as a buffer through the reversible transfer of acyl groups from CoA to form acylcarnitine, thus releasing CoA to be involved in additional metabolic reactions [7,8]. The subsequent reduction in the ratio of acyl-CoA to Co-A stimulates the enzyme pyruvate dehydrogenase, increasing the oxidation of glucose and energy production [7,8].

In patients with intermittent claudication, transient ischaemia induced by exercise may result in a state of metabolic stress, leading to an alteration in carnitine metabolism. Specifically, the incomplete oxidation of acyl-CoA, leads to an accumulation of this and its intermediates, including acylcarnitine [7,9]. As a result, carnitine levels and skeletal muscle energy supplies are depleted, limiting exercise capacity [6,7,9,10].

Correcting carnitine metabolism could therefore be an important consideration for achieving optimal walking performance in those with intermittent claudication and it has been proposed that carnitine supplementation can restore muscle carnitine stores, improve exercise capacity and consequently improve physical function in patients with PAD.

Importantly, evidence suggests that while L-carnitine is involved in metabolic function, the short carnitine esters (ALC: acetyl-L-carnitine and PLC: propionyl-L-carnitine) have a higher affinity for skeletal and cardiac muscle and hence are potentially more advantageous for therapeutic use [6]. A case for the use of PLC is further strengthened by its ability to improve endothelial function through the reduction of lipid peroxidation and xanthine oxidase activity and stimulate expression of some anti-oxidative markers in human endothelial cells [6]. The contribution of endothelial dysfunction to the pathogenesis and symptomatology of PAD has previously been identified [11].

As a naturally occurring substance, it may also avoid the side-effects, poor compliance and financial burden associated with more established treatments such as exercise and cilostazol. An