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Effect of acetyl-l-carnitine in the treatment of diabetic peripheral neuropathy: A systematic review and meta-analysis

N. Veronese [a,*], G. Sergi [a], B. Stubbs [b,c,d], the EUGMS special interest group on diabetes, I. Bourdel-Marchasson [e,f], D. Tessier [g], C. Sieber [h], T. Strandberg [i,j], S. Gillain [k], M. Barbagallo [l], G. Crepaldi [m], S. Maggi [m], E. Manzato [a]

[a] University of Padova, department of medicine, geriatrics section, via Giustiniani, 2, 35128 Padova, Italy
[b] Physiotherapy department, South London and Maudsley National Health Service Foundation Trust, London, United Kingdom
[c] Health service and population research department, institute of psychiatry, psychology and neuroscience, King's College London, London, United Kingdom
[d] Faculty of health, social care and education, Anglia Ruskin university, Chelmsford, United Kingdom
[e] Clinical gerontology department, CHU de Bordeaux, 33000 Bordeaux, France
[f] RMSB, UMR 5536, CNRS, 33400 Bordeaux, France
[g] Geriatric division, Sherbrooke university, Quebec, Canada
[h] Institute for biomedicine of aging, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nuremberg, Germany
[i] Geriatric clinic, department of medicine, university of Helsinki, Helsinki, Finland
[j] Institute of health sciences/geriatrics, university of Oulu, Oulu university hospital, Oulu, Finland
[k] Service de gériatrie, CHU de Liège, Liège, Belgium
[l] Geriatric unit, department of internal medicine and geriatrics, university of Palermo, Palermo, Italy
[m] National research council, aging branch neuroscience institute, Padova, Italy

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ABSTRACT

Background/aim: Deficiency of acetyl-L-carnitine (ALC) and L-carnitine (LC) appears to play a role in peripheral diabetic neuropathy, although the evidence in humans is still limited. We conducted a systematic review and meta-analysis investigating the effect of ALC on pain and electromyographic parameters in people with diabetic neuropathy.
Methods: A literature search in major databases, without language restriction, was undertaken. Eligible studies were randomized controlled trials (RCTs) or pre- and post-test studies. The effect of ALC supplementation on pain perception and electromyographic parameters in patients with diabetic neuropathy was compared vs. a control group (RCTs). The effect of ALC/LC on electromyographic parameters were also calculated vs. baseline values. Standardized mean differences (SMD) and 95% confidence intervals (CIs) were used for summarizing outcomes.
Results: Six articles, with a total of 711 diabetic participants, were included. Three RCTs (340 treated with ALC vs. 203 placebo and 115 with methylcobalamine) showed that ALC reduces pain perception (SMD = −0.45; 95% CI: −0.86 to −0.04; $P = 0.03$; $I^2 = 85\%$). Compared to controls, ALC supplementation improved nerve conduction velocity and amplitude response for ulnar nerve (both sensory and motor component). Compared to baseline values, ALC/LC supplementation improved nerve conduction velocity for all the sensory and motor nerves (except ulnar and peroneal) investigated and the amplitude of all nerves. The onset of adverse events was generally limited to minor side effects.
Conclusion: ALC appears to be effective in reducing pain due to diabetic neuropathy compared to active or placebo controls and improving electromyographic parameters in these patients.

1. Introduction

Peripheral neuropathy is one of the most prevalent complications of diabetes mellitus, with prevalence estimates ranging from 12 to 50% [1]. The most common form of peripheral neuropathy in diabetes is the distal symmetric polyneuropathy, a form affecting both sensory and motor nerves [1].

The complications due to diabetic neuropathy are multiple (e.g. asthenia, paresthesia in initial stages and in advanced ones ulcers and deformation of lower extremities) and often associated with higher presence of disability and poor quality of life [2]. These

* Corresponding author. Tel.: +00390498218492; fax: +00390498211218.
E-mail address: ilmannato@gmail.com (N. Veronese).

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effects are mainly due to the presence of pain, one of the most common symptoms associated with diabetic neuropathy [1].

The management of symptomatic diabetic sensory neuropathy presents a therapeutic challenge for the physicians, since the therapies for this conditions are predominantly limited to seeking to obtain good glucose control and the use of analgesic medications [3,4]. Such interventions are often not effective in symptoms and do not address the pathogenesis of diabetic neuropathy. Although the pathogenesis of this condition is not completely understood, one of the main mechanisms responsible seems to be the reduced availability of acetyl groups, necessary for the synthesis of choline [5]. A deficiency of acetyl-L-carnitine (ALC) and L-carnitine (LC) seems to play a pivotal role in this pathway [6], since a deficit of ALC has been shown to cause damage to the myelin sheath [7]. In animal models, the exogenous administration of ALC increases artemin levels and enhances the expression of nerve growth factor (NGF) [8,9], enhances antioxidant activity [10] and microvascular protein permeability [11], and induces long-term upregulation of the presynaptic mGlu2 receptors [12]; in this way, ALC supplementation induces neuroprotective, neurotrophic and analgesic effects in the peripheral nervous system [12,13].

Regarding human beings, ALC is recommended in the tier 1 of neuropathic pain treatments by the Mayo Clinic proceedings [14], and a recent meta-analysis has confirmed that administration of ALC was able to improve pain perception in people affected by peripheral neuropathy [15]. Although this work advanced our knowledge regarding this important topic, a number of limitations persist, for instance, the authors considered all kinds of neuropathies together (although they have different pathogeneses) and they did not investigate the effect of ALC on electromyographic parameters, the most common method for diagnosis and evaluating peripheral neuropathy [1].

Given the mentioned limitations in the literature, we aimed to investigate the effect of ALC on pain and electromyographic parameters in diabetic neuropathy. We hypothesized that ALC supplementation is beneficial for symptomatology and electromyographic features of diabetic neuropathy.

2. Methods

This systematic review adhered to the Prisma [16] and Moose [17] statements and followed a structured, but unpublished protocol.

2.1. Data sources and literature search strategy

Two investigators (NV and GS) independently conducted a literature search using *PubMed*, *Embase*, *Scopus*, Cochrane central register of controlled trials and Clinicaltrials.gov without language restriction, from database inception until 5th June 2016 for randomized controlled trials (RCTs) and descriptive studies (i.e. without a control group) investigating the effect of ALC supplementation in patients with diabetic neuropathy.

In *PubMed*, the following search strategy was used: "(carnitine [Text word] OR "Carnitine"[Mesh]) AND (diabet*) AND (neurop*)". Conference abstracts and reference lists of included articles were hand-searched to identify and potential additional relevant articles. Any inconsistencies were resolved by consensus with a third author (SM).

2.2. Study selection

Inclusion criteria for this meta-analysis were:

- RCTs or pre- or post-test studies;
- included diabetic participants with peripheral neuropathy diagnosed through electromyography (EMG);
- investigated the use of carnitine supplementation (regardless of administration route);
- included data regarding pain (due to neuropathy) and/or regarding EMG parameters.

Studies were excluded if:

- did not include humans;
- investigated the effect of carnitine on other causes of neuropathic pain (e.g. due to chemotherapy);
- included participants with diabetes, but without a neuropathy.

2.3. Data extraction

Two independent investigators (NV and BS) extracted key data from the included articles in a standardized Excel sheet. A third independent investigator (GS) checked the extracted data.

For each article, we extracted data about authors, year of publication, country, study design (RCT/descriptive), medications used for the treatment of diabetes, daily ALC/LC dosage, follow-up duration (in weeks) and mean age (by treatment type: ALC or control group). Finally, we extracted data regarding the adverse events reported in each study.

2.4. Outcomes

The primary outcome was the change of pain perception at follow-up assessed through a validated scale (e.g. Visual Analogue Scale) between participants treated with ALC vs. controls.

As secondary outcomes, we considered EMG parameters in terms of conduction velocity and response amplitude in terms of:

- differences between follow-up and baseline (pre and post treatment) in ALC vs. controls;
- within patients treated comparing the data at follow-up vs. baseline in people treated with ALC/LC.

2.5. Assessment of study quality

Two authors (NV, GS) completed scoring using the Jadad's scale [18] for assessing the quality and the risk of bias of the RCTs included. This quantifies the trial quality based on the description and appropriateness of randomization (2 points), blinding procedures (2 points), and description of withdrawals (1 point). A value less than 3 (over a maximum of 5) usually indicates a low-quality study at high risk of bias [19].

2.6. Data synthesis and statistical analysis

All analyses were performed using comprehensive meta-analysis (CMA) 3 and Revman 5.3. Outcomes with at least two studies were meta-analyzed, and in case of only one study, we described the data in a descriptive summary. When multiple assessments were made, the longest follow-up time was included in our analyses.

The primary analysis compared the values of pain scales between participants treated with ALC supplementation vs. controls. We calculated the difference between the means of the treatment and placebo groups using the follow-up data through standardized mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model [20].

For the secondary analysis, a similar analysis was made for ALC, whilst for ALC/LC this analysis for EMG parameters was limited to the differences between follow-up and baseline values (pre- and