Complementary therapies for peripheral arterial disease: Systematic review

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Abstract
While peripheral arterial disease (PAD) affects a considerable proportion of patients in the primary care setting, there is a high level of use of complementary treatment options. The aim was to assess the effectiveness of any type of complementary therapy for peripheral arterial disease. A systematic review was performed. Literature searches were conducted on Medline, Embase, Amed, and the Cochrane Library until December 2004. Hand-searches of medical journals and bibliographies were conducted. There were no restrictions regarding the language of publication. The screening of studies, selection, data extraction, the assessment of methodologic quality and validation were performed independently by the two reviewers. Data from randomized controlled trials, and systematic reviews and meta-analyses, which based their findings on the results of randomized controlled trials were included. Seven systematic reviews and meta-analyses and three additional randomized controlled trials met the inclusion criteria and were reviewed. The evidence relates to acupuncture, biofeedback, chelation therapy, CO2-applications and the dietary supplements Allium sativum (garlic), Ginkgo biloba (ginkgo), omega-3 fatty acids, padma 28 and Vitamin E. Most studies included only patients with peripheral arterial disease in Fontaine stage II (intermittent claudication). The reviewed RCTs, systematic reviews and meta-analyses which based their findings on the results of RCTs suggest that G. biloba is effective compared with placebo for patients with intermittent claudication. Evidence also suggests that padma 28 is effective for intermittent claudication, although more data are required to confirm these findings. For all other complementary treatment options there is no evidence beyond reasonable doubt to suggest effectiveness for patients with peripheral arterial disease.

Keywords: Peripheral arterial disease; Intermittent claudication; Systematic review; Complementary medicine; Alternative medicine

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1. Background

Peripheral arterial disease (PAD) affects a considerable proportion of the general population and is a prevalent condition in the primary care setting [1–3]. PAD is a potential threat to functional independence particularly in the elderly and is associated with hospitalisation, surgery, and death [4,5]. Treatment is usually conservative [6] and largely consists of regular physical exercise such as walking to near-maximal pain and pharmacological interventions [7–10]. In parallel, the level of use of complementary treatment options is high among the general population and patient populations [e.g., 11–14]. Prevalence data for the UK indicate that about 20–28% use complementary therapies annually and in the US, the 1-year prevalence currently amounts to about 42% [15–17]. The majority of the data suggest that herbal dietary supplements are among the most popular treatment options [11,14], which is supported by the findings of market analyses [18–20]. The US Food and Drug Administration also notes that the rapid growth of this industry will continue into the near future [21]. Thus, our aim was to assess whether any type of complementary therapy is effective for treating PAD.

2. Methods

Systematic literature searches were conducted to identify all RCTs and systematic reviews and meta-analyses of RCTs of any type of complementary therapy for treating PAD. Data sources were Medline, Embase, Amed and The Cochrane Library. The search terms used were alternative medicine, complementary medicine, dietary supplements, herbal medicine, phytotherapy, homeopathy, homoeopathy, acupuncture, osteopathy, chiropractic, peripheral arterial disease, intermittent claudication and derivatives of these. Each database was searched from its inception to December 2004. To identify additional published or unpublished studies, we conducted hand-searches in conference proceedings (PACT—Focus on Alternative and Complementary Therapies 1996–2004), our own files and relevant medical journals (Phytonmedicine 1994–2004, Alternative and Complementary Therapies 1995–2004, Erfahrungsheilkunde 1996–2004, Forschende Komplementärmedizin Klassische Naturheilkunde 1994–2004). The bibliographies of all located papers were searched for further information. There were no restrictions regarding the language of publication.

To be included, trials were required to state that they were randomized and were assessing patients with PAD. Systematic reviews and meta-analyses providing the most recently updated assessment of the evidence were included if their findings were based on the results of RCTs. Systematic reviews and meta-analyses, which did not report on separate analyses for RCTs were excluded. Also, studies assessing surrogate parameters and assessing effects on risk factors of PAD were excluded. Methodologic quality was evaluated using the Jadad scale [22]. All studies were selected and data were extracted in a systematic manner (Tables 1 and 2). The screening and selection of studies, data extraction, the assessment of methodologic quality and validation were performed independently by the two reviewers. Disagreements during this process were largely due to reading errors and were resolved through discussion.

3. Results

Seven systematic reviews and meta-analyses and three additional RCTs, which were not assessed in the reviews and meta-analyses met all inclusion criteria. The identified evidence relates to acupuncture, biofeedback, chelation therapy, CO2-applications and the dietary supplements Allicium sativum (garlic), Ginkgo biloba (ginkgos), omega-3 fatty acids, padma 28 and Vitamin E. All studies except one [23] included only patients with PAD in Fontaine stage II (intermittent claudication). Data on methodologic quality are reported in Tables 1 and 2.

3.1. Acupuncture

The literature searches identified one RCT of acupuncture for treating PAD (Table 2). Patients with unilateral lower and upper leg amputations due to PAD were included [23]. The authors suggest significant intergroup differences in favor of acupuncture (p not reported). Thus, at present little but encouraging data from rigorous clinical trials exists to suggest that acupuncture is effective for patients with PAD. Independent replication of this trial is needed. Adverse events were not reported (Table 2).

3.2. Biofeedback

One small (n = 12) RCT tested biofeedback as an adjunctive treatment for patients with intermittent claudication [24]. The treatment consisted of electromyographic feedback and skin temperature feedback from fingers and toes (Table 2). Patients also practiced muscle relaxation using a modified Jacobson/Benson technique twice daily for 20 min. There was
<table>
<thead>
<tr>
<th>First author</th>
<th>Included trials (quality (scale))</th>
<th>Intervention, Fontaine stage; n (analysed)</th>
<th>Regimen, daily dose</th>
<th>Duration</th>
<th>Control</th>
<th>Main parameter</th>
<th>Main result</th>
<th>Mean difference, (95% CI)</th>
<th>Adverse events (intervention group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villarruz [25]</td>
<td>RCTs; A to C (Cochrane)</td>
<td>Chelation therapy, II, 167</td>
<td>20 infusions of 3 g Na2 EDTA</td>
<td>5–20 weeks</td>
<td>Placebo</td>
<td>Painfree walking distance after 20 infusions</td>
<td>−16.4 m (−32.0 to −0.8)</td>
<td>Faintness, gastrointestinal symptoms, proteinuria, hypocalcemia, phlebitis, pain</td>
<td></td>
</tr>
<tr>
<td>Brockow [26]</td>
<td>RCTs; 1–2 (Jadad); 27–42 (Maastricht)</td>
<td>CO2 insufflation, II, (1) 109; (2) 102</td>
<td>12–18 insufflations of 100 to 450 ml CO2</td>
<td>3–5 weeks</td>
<td>(1) Waiting list; (2) CO2 baths</td>
<td>Walking distance</td>
<td>(1) Intergroup difference; (2) No difference</td>
<td>4 m (−35 to 43)</td>
<td></td>
</tr>
<tr>
<td>Jepson [28]</td>
<td>Double-blind RCTs; no numerical result (Cochrane)</td>
<td>Dietary supplement Allium sativum, II, 78</td>
<td>800 mg</td>
<td>12 weeks</td>
<td>Placebo</td>
<td>Painfree walking distance</td>
<td>Not reported</td>
<td>‘Severe side effects were not observed’</td>
<td></td>
</tr>
<tr>
<td>Horsch [30]</td>
<td>Double-blind RCTs (not reported)</td>
<td>Dietary supplement Ginkgo biloba, II, 619</td>
<td>120–160 mg</td>
<td>6–24 weeks</td>
<td>Placebo</td>
<td>Ratio of painfree walking distances</td>
<td>Theta 1.2 (1.2–1.3)</td>
<td>Abdominal complaints, nausea, tachycardia, headache, apoplexy, pruritis, face, hand swelling, high blood pressure, Gastrousintestinal upset</td>
<td></td>
</tr>
<tr>
<td>Sommerfield [31]</td>
<td>RCTs; 5 (Jadad)</td>
<td>Dietary supplement omega-3 fatty acids, II, 74</td>
<td>45 mg to 3 g</td>
<td>4 months to 2 years</td>
<td>Placebo</td>
<td>Painfree walking distance</td>
<td>−17.1 m (−51.4 to 17.2)</td>
<td>'Not enough evidence to determine effectiveness'</td>
<td></td>
</tr>
<tr>
<td>Melzer [32]</td>
<td>RCTs (not reported)</td>
<td>Dietary supplement Padma 28, Iib, 333</td>
<td>1.5–2.3 g</td>
<td>4 months</td>
<td>Placebo</td>
<td>Maximum walking distance</td>
<td>81.3 m (65.5–97.1)</td>
<td>Exantherma, dermatosis (1.4%), worsening of symptoms (1.4%); four serious adverse events, none of which were drug related (one death, three cases of neoplasms)</td>
<td></td>
</tr>
<tr>
<td>Kleijnen [33]</td>
<td>Double-blind RCTs; 3–7 (Kleijnen)</td>
<td>Dietary supplement Vitamin E, II, 154</td>
<td>300–900 mg</td>
<td>8–10 months</td>
<td>Placebo</td>
<td>Various exercise performance measures</td>
<td>‘Not enough evidence to determine effectiveness’</td>
<td>‘No study reported any serious side effect’</td>
<td></td>
</tr>
</tbody>
</table>

* Jadad scale, Kleijnen scale, Maastricht scale award a maximum of 5, 10, and 100 points, respectively.
* It is reported, that neither the method of randomization nor the concealment of allocation were described; no intention-to-treat analysis; inclusion, exclusion criteria were adequately reported; number of drop-outs described.

c Based on orally presented data.
no mention of intergroup differences. Compared with base-
line, maximal walking time assessed on a treadmill at an
inclination of $10^\circ$ and a speed of 3.6 km/h increased signifi-
cantly ($p < 0.001$).

3.3. Chelation therapy

Chelation therapy uses oral and intravenous administra-
tion of EDTA, usually in combination with vitamins and
trace elements to treat a variety of conditions including PAD. A
Cochrane review identified five RCTs [25] (Table 1). All
studies were performed double-blind and compared EDTA
chelation with isotonic NaCl solution or distilled water. There
were no significant intergroup differences in favor of chela-
tion therapy. For painfree walking distance after 20 infusions,
there was a significant effect in favor of control (weighted
mean difference $-16.4$ m, 95% CI $-32.0$ to $-0.8$). The re-
view concluded that there is not enough evidence to determine
the effectiveness or otherwise of chelation therapy. Adverse
events included faintness, hypocalcemia, proteinuria and gas-
trointestinal symptoms.

3.4. CO$_2$-applications

Subcutaneous CO$_2$ insufflations are being used as a treat-
ment modality in naturopathy almost exclusively in Europe.
A systematic review [26] identified three RCTs, which as-
signed patients with intermittent claudication. The data from
one trial suggested significant intergroup differences for
painfree walking distance compared with patients on a wait-
ing list, while two others reported mixed results compared
with waiting list controls and patients receiving CO$_2$-baths
($p$ not reported). Another small RCT ($n = 24$) assessed the ef-
facts of immersion in CO$_2$-containing water [27]. It reports an
increase in painfree walking distance after immersion of the
lower extremities for 30 min five times weekly for 4 weeks
compared with baseline.

3.5. Dietary supplements

3.5.1. Allium sativum (garlic)

A Cochrane review [28] of $A$. sativum extract for treat-
ing intermittent claudication identified one RCT [29]. This
trial was double-blind and placebo-controlled and included
78 patients who were treated for 12 weeks. In addition to
$A$. sativum extract, all patients received physical therapy twice
weekly. The Cochrane reviewers report that based on their
data analysis, there is no statistically significant difference
between the groups.

3.5.2. Ginkgo biloba (ginkgo)

The effectiveness of $G$. biloba extract for treating patients
with intermittent claudication was assessed in a meta-analysis
of double-blind, placebo-controlled RCTs [30]. Trials using
the standardized extract EGb 761 and measuring pain-free
walking distance were included. Nine studies, which assessed

### Table 2

<table>
<thead>
<tr>
<th>First author[reference]</th>
<th>Design; quality</th>
<th>Patients mean age (years), Fontaine stage</th>
<th>Treatment</th>
<th>Control</th>
<th>Main parameter</th>
<th>Intergroup differences</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyb [23]</td>
<td>Open, parallel; 2</td>
<td>67, II–IV</td>
<td>Acupuncture</td>
<td>Waiting list</td>
<td>Perfusion at lower extremity</td>
<td>Significant ($p$ not reported)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Greenspan [24]</td>
<td>Open, parallel; 2</td>
<td>58, II</td>
<td>Biofeedback</td>
<td>Waiting list</td>
<td>Maximal walking time (inclination $10^\circ$, speed 3.6 km/h)</td>
<td>Not reported. $p &lt; 0.001$ compared to baseline</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hartmann [27]</td>
<td>Open, parallel; 1</td>
<td>65–68, II</td>
<td>CO$_2$-water</td>
<td>Flush water</td>
<td>Painfree walking distance (flat ground, speed 120 steps/min)</td>
<td>Significant ($p$ not reported)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*a Jadad scale awards a maximum of five points.*
independent replication is required. The sizes of the single trials presented in Table 2 are small and effectiveness beyond placebo for patients with PAD. There is no evidence beyond reasonable doubt to suggest their effectiveness, for all other complementary treatment options there is no evidence of improved clinical outcomes in patients with intermittent claudication.

3.5.5. Vitamin E

A Cochrane review assessed the evidence for Vitamin E and identified three double-blind RCTs [33]. The reviewers report that the trials were small and generally of poor quality. The authors concluded that there is insufficient evidence to determine whether Vitamin E is effective for treating patients with intermittent claudication. The meta-analysis of two trials reporting similar dosage and duration of treatment, which however, included one trial that was not randomized, suggested a relative risk of 0.6 (95% CI 0.3–1.2) for patients’ subjective evaluation of the treatment.

4. Discussion

The reviewed data from RCTs, systematic reviews and meta-analyses, suggest that G. biloba extract is effective compared with placebo for patients with intermittent claudication (PAD Fontaine stage II). Evidence also suggests that padma 28 is effective, yet more data are required to confirm these findings. For all other complementary treatment options there is no evidence beyond reasonable doubt to suggest their effectiveness beyond placebo for patients with PAD. The sample sizes of the single trials presented in Table 2 are small and independent replication is required.

For G. biloba, this conclusion is corroborated by an earlier meta-analysis [34]. In this study, the difference of the change of painfree walking distance was 34 m (95% CI 26–43) in favor of G. biloba compared with placebo. Sensitivity analyses of trials using similar methodology and of those scoring highest for methodological quality corroborate the main result. A walking speed of less than 3 km/h on flat ground – in contrast to the speed and inclination in most trials using ergometers – may further increase painfree walking distance. Other pharmacological interventions for intermittent claudication, which are approved by the FDA include pentoxifylline and cilostazol [9,35,36]. An early meta-analysis of RCTs testing pentoxifylline suggests a mean difference in the increase of painfree walking distance of 57% compared with placebo [37]. In another meta-analysis, this difference was 21 m for painfree walking distance and 44 m for maximal walking distance [38]. A double-blind RCT suggested a similar increase in painfree and maximal walking distance for pentoxifylline and G. biloba extract [39]. Cilostazol also seems efficacious when compared with placebo [40,41]. However, the increase of painfree walking distance with regular physical exercise is substantially larger than for oral treatments. It has been reported to range between 88 and 190% from baseline [42,43]. A meta-analysis suggested a significant average increase of painfree walking distance of 139 m in favor of exercise training compared with placebo or no intervention [38]. One disadvantage of exercise therapy for intermittent claudication lies, of course, in the notoriously poor compliance with such programs.

The notion that G. biloba is effective for intermittent claudication is supported by its pharmacological actions. The main active principles are bilobalide and ginkgolides [44]. The latter, in particular ginkgolide B, inhibits platelet activating factor [45]. Other actions include a decrease in erythrocyte aggregation and blood viscosity as well as anti-ischemic effects through the increase of trancutaneous partial pressure of oxygen [e.g., 46]. In vitro experiments suggest that the vasorelaxing effects of G. biloba extract are related to the release of nitric oxide which, in turn, may be influenced by the free radical-scavenging activity of the extract [44]. The relative importance of these actions for the clinical effects of G. biloba is, however, uncertain at present.

We aimed to identify all RCTs, and all systematic reviews and meta-analyses based on RCTs of any type of complementary therapy for treating PAD. The potential incompleteness of the citation tracking is one of the limitations of this systematic review and indeed systematic reviews in general. Although strong efforts were made to locate and retrieve all trials on the subject, it is conceivable that some were not uncovered. Restrictions of literature searches relating to the language of publications and databases are problematic. For this review we searched databases with a focus on the European and American literature and one that specializes in complementary medicine. There were no restrictions in terms of publication language. We are therefore confident that our search strategy minimized bias. The appraisal of the evidence involved a degree of judgement and is another potential source of bias. However, for individual RCTs we used a standard
scale [22] to assess important criteria of methodologic quality (Table 2). This scale was also used in two of seven systematic reviews and meta-analyses (Table 1). The methodologic quality of the evidence was combined in an informal process with the type of evidence (e.g., RCT, meta-analysis) and the volume of evidence to produce an indication of weight. This process of appraising the clinical evidence was performed independently by the two reviewers, which further minimized bias.

In conclusion, the available data from RCTs, and systematic reviews and meta-analyses which based their findings on the results of RCTs suggest that *G. biloba* is effective compared with placebo for patients with intermittent claudication. Evidence also suggests that padma 28 is effective in patients with PAD. For all other complementary treatment options there is no evidence beyond reasonable doubt to confirm these findings. For all other complementary treatment options there is no evidence beyond reasonable doubt to suggest effectiveness for patients with PAD.

References


