

Leg ulcers (arterial/venous): oral zinc supplementation and healing

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Author

The Wound Healing and Management Node Group

Question

What is the best available evidence regarding the effectiveness of oral zinc supplementation in healing arterial or venous leg ulcers?

Clinical bottom line

The recommended daily allowance for zinc in healthy adults is between 8 and 15 mg per day; this is usually provided by a well-balanced diet. At the systemic level, zinc serves as a cofactor in numerous transcription factors and enzyme systems including zinc-dependent matrix metalloproteinase that augment auto-debridement and keratinocyte migration during wound repair^{1,3} (Level I & III respectively).

Patients with chronic leg ulceration are commonly found to have low serum zinc levels or abnormal zinc metabolism. At the biochemical level, zinc deficiency is defined by a serum zinc level below 9 mmol/L; however, the presence of additional comorbidities may also contribute to a zinc deficiency¹ (Level I). Zinc deficiency is treated with oral zinc sulphate at 30 to 150 mg per day² (Level I).

Recent reviews have generated little evidence for the effectiveness of oral zinc supplementation on the healing of arterial and venous ulcers^{1,2} (Level I) ³(Level III). More good-quality trials of a larger scale are needed to establish the effectiveness of oral zinc supplementation to aid healing of leg ulcers¹⁻³ (Level I). One review suggests that topical zinc is superior to oral zinc sulphate in augmenting venous leg ulcer healing by its anti-infective action and its promotion of auto-debridement and epithelialisation¹ (Level I).

Diagnosing zinc deficiency is complicated by a number of factors, including the sensitivity of the measuring device. In addition, normal serum zinc levels do not necessarily indicate that adequate zinc is being delivered to a wound; expert opinion maintains that evidence for zinc deficiency can really only be determined by a clear clinical response to zinc therapy under controlled conditions¹ (Level I).

The following healing outcomes have been associated with topical application of zinc oxide¹ (Level I):

- Contribution to the healing of leg ulcers.
- Acts as an enzymatic topical debriding agent in pressure ulcers and burns.
- Contribution to healing in diabetic foot ulcers when applied in a zinc oxide-medicated occlusive dressing.

- Beneficial in wounds healing primarily by epithelisation.
- The antiseptic property of zinc oxide was demonstrated by frequently less culture counts of *Staphylococcus aureus* in wounds treated with zinc oxide compared to placebo-treated wounds.

Signs and symptoms

Signs and symptoms of zinc deficiency include the following^{1,2} (Level I):

- ataxia
- depression
- impaired taste
- anorexia
- diarrhoea
- eczematous dermatitis
- alopecia
- mouth ulcers
- delayed wound healing
- more prone to infections.

Risk factors

Topical zinc oxide is usually well tolerated and reports of hypersensitivity are rare. However, sensitivity to preservatives or alcohol associated with some dressings has been reported¹ (Level I).

Side effects of taking oral zinc supplementation were reported in two systematic reviews. At a dosage level of 220 mg, three times a day, the following side effects were reported¹ (Level I):

- abdominal pain
- dyspepsia
- nausea
- vomiting
- diarrhoea.

At a dosage level between 440 and 660 mg per day, the following side effects were reported² (Level I):

- dizziness
- constipation
- nausea after a few weeks of treatment.

Characteristics of the evidence

This evidence summary is based on a structured search of the literature and selected evidence-based health care databases. The evidence in this summary is from:

- A metasynthesis of research summarising the physiological and pharmacological roles of zinc in the wound-healing process¹.
- A systematic review, including six randomised controlled trials containing 183 participants².
- Four of these trials assessed people with venous ulcers; one trial assessed people with arterial ulcers; and one trial assessed people with mixed ulcers.
- Treatment duration and participant follow-up varied amongst the studies; due to this diversity the results could not be combined for analysis.
- A cross-sectional observational study conducted with overweight/obese participants³.

levels may provide a more reliable assessment of zinc deficiency despite normal zinc serum levels (Grade B).

- Zinc deficiency is treated with oral zinc sulphate at 30 to 150 mg per day (Grade B).
- Topical zinc applications may be more effective than oral zinc supplementation in the healing of chronic leg ulcers (Grade B).

References

1. Lansdown ABG, Mirastschijski U, Stubbs N, Scanlon E & Ågren MS. Zinc in wound healing: Theoretical, experimental, and clinical aspects. *Wound Repair Regen* 2007; 15:2–16. (Level I).
2. Wilkinson EAJ & Hawke CC. Oral zinc for arterial and venous leg ulcers. *Cochrane Database Syst Rev*. 1998:4 (Updated 2009). (Level I).
3. Tobón J, Whitney JD & Jarrett M. Nutritional status and wound severity of overweight and obese patients with venous leg ulcers: A pilot study. *J Vasc Nurs* 2008; 26:43–52. (Level III).

Best practice recommendations

- Assessing patients' dietary intake in addition to serum zinc

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