

Wound healing: is oral zinc supplementation beneficial?

This review critically summarises the available literature on the role of zinc in wounds and explores whether evidence exists to support the beneficial effects of oral zinc supplementation in wound healing. The function of zinc in the normal wound-healing process is acknowledged as being evident throughout the inflammatory and proliferative stages. However, the evidence regarding oral zinc supplementation is generally inconclusive. Findings suggest that further research could demonstrate a place for supplementation in zinc-deficient patients, but more rigorous patient-centred trials are necessary to support a significant change in clinical practice.

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KEY WORDS

Zinc supplementation
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Nutrition and diet
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Nutrition is an important extrinsic factor influencing wound healing, and malnutrition has an adverse effect on a wound's ability to heal efficiently and effectively (Barbul and Purtill, 1994; Pontieri-Lewis, 1997; Carlson, 1999). The significance of thorough nutritional assessment in the prevention and treatment of acute and chronic wounds is widely accepted (George and Bugwadia, 1996; Flanigan, 1997), and yet it is often considered a low priority in the clinical setting (Gray and Cooper, 2001).

A growing proportion of the available nutritional literature considers the importance of trace elements and minerals, throughout the wound healing process, alongside the acknowledged role of macronutrients (Berger and Shenkin, 1998; Todorovic, 2002). Zinc is

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identified as a major trace element in the wound-healing process because of its involvement in many different cellular processes (Gray, 2003; Collins, 2003). This article aims to discuss and review the available literature regarding the influence of zinc in wound healing, and whether zinc supplementation is a necessary requirement to promote healing.

Literature was obtained by searching the Medline, British Nursing Index, CINAHL and Embase databases via Ovid, and also PubMed. The key terms used were 'zinc', 'wound healing', 'pressure sores' and 'leg ulcers', both separately and then in combination. This yielded a mixture of randomised and non-randomised clinical trials, laboratory experiments and systematic reviews. Further studies were identified from the references cited in these papers. No limit was set on the dates for the published literature. A significant amount were pertinent trials conducted from the 1960s which required review alongside more recent work. The Cochrane Database of Systematic Reviews was also searched for systematic reviews involving zinc and wound healing.

The function of zinc

Wound healing is a complex process involving the stages of inflammation, proliferation and maturation that occur on a continuum from injury to healing (Scholl and Langkamp-Henken, 2001).

For optimum wound healing these stages must be progressed through smoothly and efficiently, and zinc has an identifiable role in all three stages.

Zinc is the second most abundant trace metal found in the human body (Lansdown, 1996), and has many functions. It is mainly stored in erythrocytes and leukocytes, but is also found in muscle, bone, skin and other organs (Prasad, 1979). Some zinc exists as free ions, but over 95% of total body zinc is bound to proteins within cells and cell membranes. In the plasma, approximately 30–40% of zinc is bound to α_2 -macroglobulin or transferrin, 60% to albumin and 2% to amino acids (Russell, 1980). The main form that zinc takes in the cellular environment is as part of metalloenzymes and is involved in the stimulation of multiple enzyme pathways (Collins, 2003).

On a basic, but critical, cellular level, zinc is necessary for deoxyribonucleic acid (DNA) synthesis and replication, and therefore is essential for growth (Gray, 2003). Zinc is involved in haemostasis through its interaction with platelets, and is necessary for antibody production and immune cell function (Collins, 2003). McLaren (1992) suggests it also inhibits bacterial growth. Zinc plays a central role in the proliferation of inflammatory cells and modulates cutaneous inflammation (Tenaud et al, 1999).



Throughout the proliferation and maturation phases, zinc is required for collagen synthesis. The element is also necessary for the proliferation of fibroblasts and keratinocytes and quickens the process of re-epithelialisation, while strengthening the wound (Tenaud et al, 1999; Todorovic, 2002).

The influence of zinc on wound healing

Although it is generally considered throughout the literature that zinc does influence the wound-healing process (Agren, 1993; Sullivan et al, 1999; Kohn et al, 2000), the exact mechanisms for this are unclear. In addition, the evidence for the supplementation of zinc to aid healing is conflicting.

Zinc and sinus healing

A study by Pories et al in 1967 was the first to look at the influence of zinc in the healing of human wounds. Previous encouraging work with zinc and rats led to this trial of zinc supplementation in 20 young healthy airmen following excision of chronic pilonidal sinuses. The participants were randomly allocated either to a treatment group where they received 220mg of zinc sulphate three times daily, or to a control group where no medication was received. Healing was assessed through measurement of changes in wound volume giving a rate of wound closure. Complete healing was defined as re-epithelialisation.

Results indicated that wounds healed in 80.1 ± 13.6 days in the control group and in 45.8 ± 2.6 days in the treatment group. Rate of wound closure was 0.44ml/day in the control group and 1.25ml/day in the zinc-treated group. This indicated that zinc supplementation had a beneficial effect on wound healing.

The authors acknowledged that the study was susceptible to bias because of not being double-blinded, but explained that this was due to a lack of knowledge of the effects of oral zinc sulphate administration at the time of the study. This would seem reasonable from an ethical viewpoint but did necessitate the need for further methodologically sound research in order to draw valid conclusions. Differences in baseline sizes of the sinuses also introduced an

element of bias because of wounds not healing at the same rate, but this was favoured towards the control group as their wounds were of a smaller size. This could indicate some evidence to support the results as, despite the bias, the treatment group still showed quicker healing times and rates.

Assumptions were also made that the study participants were taking their medication properly as no serum zinc measurements were taken or similar evidence of treatment compliance presented. Despite methodological flaws, this study was useful as it demonstrated the need for further research into the area and prompted subsequent trials.

Zinc and skin complaints

Greaves and Boyde (1967) conducted a preliminary study looking at the plasma zinc concentrations of patients suffering with psoriasis, other dermatological conditions and venous leg ulceration. They found that patients with these conditions had a statistically significant decrease in plasma zinc levels compared to a control group with no existing skin conditions. Withers et al (1968) completed a similar study and found no difference in plasma zinc concentrations in patients with psoriasis, but found that those with chronic venous leg ulceration had significantly lower levels than controls.

Zinc and leg ulcers

These results led to Greaves and Skillen undertaking a trial in 1970 to determine the effect of long-term zinc supplementation on the healing of chronic venous leg ulcers. Again, 220mg of zinc sulphate was given three times daily, but this time plasma zinc was monitored pre- and post-treatment. Healing was determined using measurements of ulcer area, which were used to calculate linear re-epithelialisation over time.

Results indicated again that baseline plasma zinc concentrations are reduced in patients with leg ulcers. However, despite increases in these levels with zinc supplementation, the study failed to find a correlation between healing rates and zinc levels. Nevertheless, all 18 subjects displayed evidence of re-epithelialisation, 13 of which

achieved complete healing, despite having suffered with the ulcers for at least 2 years previously. This could indicate some effect from the zinc sulphate.

This study, however, was fundamentally flawed in that it used no control group to compare rates of healing without zinc supplementation and so the results have diminished significance. The sample size was also small, casting doubt over the generalisability of the results to a bigger population. In addition, no mention is made of control over confounding variables or baseline differences, which could introduce bias.

Myers and Cherry (1970) also found no difference between the healing rates of patients receiving zinc supplementation and a control group, but again the trial was not rigorously conducted. Assumptions were made that wounds heal at the same rate over time, and different elements of bias were introduced through differences in ulcer size and follow-up time between the groups.

A small trial conducted by Hallbook and Lanner in 1972 looked at healing in patients with chronic venous ulcers who were given either a zinc supplement or a placebo. The trial had a small sample size of 27 patients, which was due mainly to the strict exclusion criteria because of difficulties relating to assessment of healing with different-sized ulcers. This, however, did decrease the risk of bias of differing healing rates. Also, despite mentioning that patients were randomised, no explanation is given of how this was performed leading to doubts of possible bias and poor reliability.

The participants were given 200mg of zinc sulphate three times daily and serum zinc levels were monitored pre-treatment. Ulcer area was determined weekly, and photographs taken at 6 and 12 weeks to assess ulcer healing. The trial had the advantage of being double-blinded to reduce bias during the assessment and analysis stages.

Analysis of the results was separated into two groups — those who had below normal serum zinc levels at



the start of the trial and those whose levels were normal or high. The results suggest that zinc supplementation has no effect on the healing of patients with normal zinc levels, but an improvement was seen in patients with pre-existing zinc deficiency. A systematic review of the effect of zinc supplementation on venous ulcers conducted by Wilkinson and Hawke (1988) supports this finding.

Laboratory experiments on zinc supplementation

More recently, experiments have been conducted on animal models to look at the effect of zinc on a more basic cellular level at different stages of the wound-healing process.

Lansdown et al (1999) attempted to determine the sequential changes in zinc concentration (alongside the other trace metals metallothionein and calmodulin) in an incisional wound in rats. The study was thorough and detailed in its explanation of scientific techniques used, which improves reproducibility, and results indicated good validity by addressing the original question. Wounding was also standardised well to decrease risk of bias. Full-thickness surgical wounds were inflicted on anaesthetised rats who were then euthanised at different periods between one and 10 days. During autopsy, the wound sites were excised and samples taken for trace metal analysis using atomic absorption spectrophotometry.

Results indicated that zinc concentrations increased at the wound site until the fifth day before decreasing over the next five days. Metallothionein, an intracellular metal-binding protein that has a particular affinity to zinc, was used as a marker for modulation of trace elements. Increased metallothionein reactions were seen at the wound site during the early influx of inflammatory cells and during collagenesis, which, the authors suggest, indicates the need for zinc at this time for repair.

The study concluded that wound healing would be adversely affected if the uptake of trace elements were impaired. Awareness should also be made of the interaction of trace

elements with one another and the effect this can have on healing. This could be important from a clinical perspective when considering using zinc-medicated dressings. It suggests that zinc is required more in the earlier rather than the later stages of healing, and using it beyond that could alter the function of other trace elements within the wound and actually impair rather than promote healing.

Lim et al (2004) propose that the antioxidant role of zinc is affected when inadequate levels are present, leading to increased oxidative stress-induced tissue damage. This...in turn decreases the expression of cytokines necessary for neutrophil infiltration and tissue repair.

Lim et al (2004) also investigated the effect of zinc on the early inflammatory phase of wound healing in mice. The study was presented well with clearly defined hypotheses and outcome measures. It incorporated a thorough methodology using referenced scientific techniques, which gives evidence of good reliability and validity. A control group was used for comparative reference and baseline differences and other confounding variables were controlled in order to reduce bias and improve reliability of findings. The main concern is that as the study was performed on mice, the findings cannot necessarily be extrapolated to humans.

The basis for the study was the stimulation of neutrophil recruitment by interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α), which is regulated by a transcription factor, nuclear factor κ B (NF κ B). It was hypothesized that zinc promotes wound healing through its action on NF κ B, which is involved in regulating the inflammatory response.

Full-thickness cutaneous wounds were inflicted on mice that were then either fed a zinc-deficient diet or supplemented with 500 μ g or

1000 μ g of zinc per gram of a specified powder diet for 2 weeks. Serum and skin zinc concentrations were assessed, wound closure measured and biopsies taken to assess influx of neutrophils and inflammatory mediators into the wounds. It was found that wound-closure rate, presence of neutrophils and expression of inhibitory messenger RNA, IL-1 β and TNF- α was significantly increased in mice receiving 500 μ g/g zinc diet when compared to both the zinc-deficient diet mice and also the mice receiving the higher dose of zinc. This led to the conclusion that supplementing dietary zinc at 500 μ g/g has a positive effect within the inflammatory stage of wound healing, but that high-dose zinc actually has a negative effect.

This study was particularly interesting as again it attempted to explain how zinc affects healing, whereas older research is more intent on proving whether or not a relationship actually exists. Lim et al (2004) propose that the antioxidant role of zinc is affected when inadequate levels are present, leading to increased oxidative stress-induced tissue damage. This reduces the effect of NF κ B that, in turn, decreases the expression of the cytokines necessary for neutrophil infiltration and tissue repair.

Zinc and surgical wounds

Finally, Zorrilla et al published a study in 2004 that looked at using serum zinc levels as a prognostic tool for delayed wound healing in 97 patients who had undergone hip hemiarthroplasty surgery. Preoperative serum zinc levels were measured and postoperative wound healing was assessed using predefined parameters to diagnose delayed healing.

Thirty study participants were diagnosed with delayed healing and statistical tests demonstrated a significant correlation with low zinc levels in these patients compared with the group with no healing problems. The authors concluded that low serum zinc levels will predict delayed wound healing with a sensitivity of 80%, which they considered could indicate a place for preoperative zinc supplementation in patients undergoing elective surgery.

The conclusions drawn seem reasonable in view of the fact that the study had sound methodology with good controls using standardised surgical techniques. Bias was reduced through analysis of demographic variables in patients to reduce baseline differences and because the wound-healing assessment was performed by one person who was blinded to the serum zinc levels. However, further research would be appropriate before a change in practice is instigated.

Zinc toxicity

It has also been acknowledged within the literature that excess zinc can have a detrimental effect on wound healing. The previously examined study by Lim et al (2004) found that high-dose zinc delayed healing, and a suggestion was made based on previous research that this was due to increased zinc intake decreasing copper absorption. Lansdown (1996) states that copper is important because of its role in collagen cross-linking and that an interaction between the two elements adversely affects the role of both. Gray (2003) reports that excessive zinc can induce both iron and copper-deficient anaemias, which could result in decreased oxygen delivery to the wound.

A study by Chandra (1984) found that men receiving 150mg of oral elemental zinc twice daily for 6 weeks displayed evidence of impaired neutrophil and lymphocyte function. Haggard et al (1998) identified adverse effects from 100mg elemental zinc sulphate daily in older patients with pressure ulcers compared to a control group. They concluded that zinc supplementation increased gastrointestinal disturbances and the risk of an infection. This could support Chandra's (1984) findings that increased zinc decreases immune function.

It must be noted, however, that in the initial studies reviewed earlier no evidence of zinc toxicity was found when patients were receiving similar doses. This suggests the need for further study, but that caution is required when considering zinc supplementation.

Discussion

It has been demonstrated that research regarding the role of zinc in wound healing is, on the whole, inconclusive.

Conclusions are difficult to draw, particularly in the case of zinc supplementation and wound healing because of multiple barriers in performing this type of research. Berger and Shenkin (1998) state that technical difficulties, such as contamination during sample collection, are inherent to trace element research, and also that there is often a large patient intervariability.

Zinc has been shown to play a significant part in the wound-healing process, but the evidence for routine zinc supplementation is poor.

Interpreting zinc status using current laboratory tests is also difficult. Serum zinc is often used, which is not particularly reliable because of the albumin-binding property of zinc (Scholl and Langkamp-Henken, 2001; Collins, 2003; Gray, 2003). Control groups and zinc-supplemented groups often have similar pre- and post-trial serum zinc levels, suggesting blood is only a transition compartment for zinc. Therefore, serum levels may not accurately reflect actual zinc status (Berger and Shenkin, 1998). Also, hypoalbuminaemia may occur as a result of the inflammatory processes naturally occurring during wound healing, giving misleadingly low serum zinc levels which do not accurately measure for true zinc deficiency (Carlson, 1999).

Fell and Talwar (1998) point out that measurements of extracellular concentrations of micronutrients are indirect and insensitive when one considers that most exert their biochemical functions intracellularly. Zinc status is also difficult to assess because of the body's strict homeostatic control of zinc absorption and excretion. This can maintain normal zinc balance even when intake is lower than recommended amounts, making

deficiencies hard to detect (Andrews and Gallagher-Allred, 1999).

Collins (2003) states that conducting randomised controlled trials that identify zinc as the only significant factor in wound healing, is troublesome. Deficiencies are often multiple (Barbul and Purtill, 1994), and availability and function of zinc can also be affected because of the interaction with other trace elements, especially those that compete for absorption in the intestines (Hardy and Reilly, 1999).

Differences in the form of zinc supplementation used makes comparison between trials at times impossible. Hardy and Reilly (1999) discuss the importance of considering the form in which supplements are administered — availability, utilisations and toxicity of trace elements can be affected by the oxidation states of both the element and the counter-ligand. Allen (1998) states that there are large variations in the relative solubility of zinc salts, and that solubility should be strongly related to absorbability.

The fact that zinc sulphate and chloride are very soluble suggests that these forms are more likely to be absorbed orally than the nearly insoluble carbonate and oxide salts. Zinc absorption can also be affected if consumed with food, especially if the diet is high in phytates. Phytates are a constituent of many plant sources, such as cereals, nuts and legumes (Gray, 2003) which are known to inhibit zinc absorption profoundly (Allen, 1998). This is often a factor that is not controlled for or not mentioned in many of the trials on zinc supplementation and wound healing. A dearth of evidence on the bioavailability of zinc supplements, however, contributes to a lack of understanding of this issue, and the ability to draw precise conclusions.

These issues must be acknowledged when reviewing the accuracy of the study methods of trials involving zinc and its availability for wound healing.

Zinc has been shown to play a significant part in the wound-healing process, but the evidence for routine

Key Points

- ▶▶ Zinc is a significant trace element in the wound healing process due to its multiple functions on a cellular level.
- ▶▶ The evidence to support routine oral zinc supplementation is generally poor and inconclusive.
- ▶▶ Some evidence suggests oral zinc supplementation may have a beneficial effect on wound healing in patients who have an existing zinc deficiency.
- ▶▶ Some trial findings suggest excess zinc might actually impair wound healing.
- ▶▶ Larger, more rigorous patient-centred trials are required to draw more accurate conclusions.

zinc supplementation is poor. There appears to be more support for supplementing zinc-deficient patients in order to improve wound healing. This was also the conclusion of a Cochrane systematic review conducted by Wilkinson and Hawke (1998) on oral zinc in patients with leg ulcers, although the review acknowledged the weakness of the evidence.

The overall research into zinc and wound healing is, although extensive, riddled with flawed methodologies. The trials use small samples and no effort is made to calculate the numbers needed, and the dropout rate is frequently high. Risk of bias is evident throughout the study designs and length of follow-up is often short, which decreases the likelihood of gaining a true effect of the intervention.

The majority of the research cited in this article is, although useful, old, but the more recent research is laboratory based using animal models, rather than good quality trials on patients. This review has definitely highlighted a need for more studies with rigorous methodologies if conclusive results are to be gained. It also reinforces the necessity for thorough nutritional assessments, including evaluation of trace elements and minerals, in order to optimise wound healing. **WUK**

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