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Title
Effectiveness of zinc therapy for the treatment of pressure ulcers

Commentary on: Song YP, Wang L, Yu HR, Yuan BF, Shen HW, Du L, Cai JY, Chen HL. Zinc Therapy Is a Reasonable Choice for Patients With Pressure Injuries: A Systematic Review and Meta-Analysis. Nutr Clin Pract. 2020 Dec;35(6):1001-1009. doi: 10.1002/ncp.10485. Epub 2020 Mar 13. PMID: 32166790.

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Conflict of interest statement
The authors declare no conflicts of interest.

Abstract
Pressure ulcers are a significant burden in healthcare settings, impacting patients' lives and incurring substantial costs. Nutrition, including the micronutrient zinc, plays a role in wound healing. However, controversy exists regarding zinc supplementation for pressure ulcer management. Further research is needed to determine the efficacy, optimal dosages, and safety of oral zinc supplementation. This commentary provides a critical appraisal of the systematic review conducted by Song et al. (2020) which evaluates the efficacy of zinc therapy in the treatment of pressure sores, focusing on the implementation of the nutritional recommendations in context to practice.

Key Points

- There is some tentative evidence that zinc therapy may improve healing rate, healing area and improve Pressure Ulcer Scale for Healing (PUSH) scores for adults with a pressure sore.
- Further high-quality research is required for both oral zinc therapy and its topical application.
- Further research should explore possible moderating factors of duration, frequency and mode of delivery.

Introduction

Decubitus ulcers, also known as bedsores or pressure ulcers (PUs), result from the prolonged or constant application of pressure on the skin, leading to damage in both the skin and underlying tissues (Zaidi et al. 2023). It is well known that pressure ulcers cause a major burden within hospitals and community settings worldwide (Afzali Borojeny et al. 2020; Zhang et al. 2021). An estimated 1/1000 community dwelling patients within the United Kingdom have a Grade 1 pressure sore and above (Stevenson et al. 2013). Pressure sores can affect all aspects of an individual's life and are associated with increased stress, depression, reduced quality-of-life, social, and financial status (Charalambous et al. 2018; Galhardo et al. 2010; Langemo et al. 2000). It has been estimated that the NHS spends about £8.3 billion on wound care management per year (Julian et al. 2020) with individual costs for treatment ranging from £1,214 (Grade 1) to £14,108 (Category 4) (Dealey et al. 2012).

The aetiology of pressure injuries is varied with a wide range of intrinsic and extrinsic factors (Agrawal and Chauhan 2012). It has been suggested that nutrition plays a key role regarding the development and healing of pressure sores (Saghaleini et al. 2018). Physiologically, our body needs both macro and micronutrients for a wound to heal (Manley and Mitchell 2022). Zinc is a micronutrient involved in the epithelialisation and formation of granulation tissue and it is a contributor to protein synthesis, vital for skin regeneration (Lin et al. 2017).

There is controversy in relation to the supplementation of minerals in the management of PUs, especially regarding zinc (Saghaleini et al. 2018; Song et al. 2020). A systematic review undertaken by Song et al. (2020) explores the use of zinc therapy and its association with wound healing.

Aim of commentary

This commentary aims to critically appraise the methods used within the review of Song et al. (2020) and expand upon the findings in the context of clinical practice.

Methods of Song et al. (2020)

An adequate multi-database search was undertaken on Embase, Web of Science and MEDLINE from the date of inception to September 2019. Only randomised and non-randomised studies which reported in full comparing zinc therapy to usual care, with a sample size of <20 people with a pressure injury (National Pressure Ulcer Advisory Panel definition) were included. The method regarding the abstract, title and full paper screening was unclear. Data extraction was undertaken by two reviewers; however, it is unclear if this was independent from each other. A meta-analysis was undertaken using a fixed effects model when I^2 was less than <50%. When the I^2 statistic was >50% a random effects model was utilised. Publication bias was assessed using a funnel plot.

Results of Song et al. (2020)

After duplicate removal, a total of 1,025 studies were identified. After screening, seven studies were included in the review. Out of the seven studies, six were randomised and one non-randomised. Two out of the six randomised controlled trials (RCTs) were classified to be of low risk of bias. The remaining four RCTs were classified to be of unclear risk of bias. Only three studies reported duration of treatment ranging from one to 13 weeks.

All included studies reported a statistically significant improvement in healing of pressure injury. When a meta-analysis was carried out it was found that there was a statistically significant increase of healing rates in the group receiving zinc compared to control (Relative Risk, 1.44, 95% confidence interval 1.01 to 2.06, I^2= 19.3%). An inadequate evaluation of publication bias was conducted for this outcome due to the inclusion of more than 10 studies. However, it was concluded that there was no sign of publication bias.

Regarding the healing area, all three studies demonstrated statistically significant improvement. Out of these three-studies zinc therapy was delivered using specific nutrition intervention, PI area polarizing medicine and Oral formula (oral formula enriched with arginine, zinc, and antioxidants). Two studies reported statistically significant improvement in PUSH score.

Commentary

Using the AMSTAR 2 tool this review achieved eleven out of sixteen criteria (Shea et al. 2017). The main strengths of the methods used in this review were that there was a clear and robust inclusion criterion, the review used a comprehensive multi-database search, a risk of bias for all included studies was undertaken and an appropriate method of synthesis was used for the meta-analysis. Regarding the main methodological weaknesses of the review, the criteria for justification of study design were unclear. This lack of clarification could introduce additional bias in the study selection. There was also lack of clarity regarding the independence of the screening process which may have introduced possible selection bias. The current gold standard for this approach is to undertake this process with two reviewers independently (Lefebvre et al. 2019). There were also further reporting issues regarding the describing of funding sources. Whereas this may not directly impact the methodological robustness of the systematic review synthesis process, it is important to acknowledge the funding bodies of the included studies, as this may influence the interpretation of the findings (Khamis et al. 2018). Furthermore, if there are an adequate number of studies this possible bias may be assessed within a subgroup/sensitivity/meta-regression assessment (Faggion et al. 2014). In relation to the meta-analysis, there was no interpretation of the individual risk of bias of the included studies for each outcome. Thus, it is unclear what the individual risk of bias of each study may have on each outcome/estimate reported within this review.

Even though not acknowledged in the AMSTAR 2 tool, there are possible issues of reporting bias, with missing outcomes which were acknowledged in Table 1, but were only partially reported in Table 2 regarding the results for these outcomes. Based on these methodological limitations, it is deemed that this systematic review may still provide an accurate and adequate summary of the results of the available studies that address the question of interest.

It is important to note when interpreting the outcome of healing rates that the majority of studies in the review were using topical zinc treatment only, making it difficult to interpret the effects of oral zinc on healing rates. In terms of indirectness, this would indicate a decreased level of confidence in the available evidence concerning the impact of oral zinc consumption (Guyatt et al. 2011b). Furthermore, when interpreting the results regarding indirectness, it is crucial to consider that the study population primarily consisted of individuals with Grade 2-4 pressure ulcers. It is possible that these findings may have diminished external validity when applied to patients with a Grade 1 pressure sore. Additionally, the presence of inconsistent intervention periods adds to the complexity of interpreting and assessing the external validity of these findings. Regarding the imprecision of the estimates presented in this review there were some concerns, as despite this effect being borderline statistically significant, it is not clinically significant, as the lowest confidence interval (no difference between intervention and control) would suggest a different recommendation to treatment compared to the higher 95% confidence interval. In context to assessing the certainty in the evidence this imprecision would suggest a reduced certainty within the estimation of healing rates presented in this review (Guyatt et al. 2011a). Therefore, even though this review suggests that zinc therapy may be effective in increasing the healing rates, the estimates presented may be substantially different than the true effect. Thus, making it difficult to make any direct recommendations to community nursing practice.

Unfortunately, for the two secondary outcomes, a meta-analysis was not able to be undertaken but there was tentative and directional evidence that nutritional support treatments help to reduce healing area and improve PUSH score, but the evidence is limited and less certain. Unfortunately, this review did not look at the possible adverse events of both oral and topical zinc therapy. Although zinc is typically

perceived to be a safe oral supplement in regulated doses (Plum et al. 2010), large amounts or chronic use may have some notable side effects such as diarrhoea, anaemia, or copper deficiency (Rabinovich 2023). The National Institute for Health and Care Excellence guidelines for practice currently do not identify zinc therapy as a recommended treatment for pressure sores (National Institute for Health and Care Excellence 2014). Although they do suggest adults can be offered a nutritional assessment by somebody with the necessary skills and competencies in this area. Subsequently, for those who have been identified to have a nutritional deficiency they may be offered additional nutritional supplements. However, the guideline indicates that this should not be recommended to those with an adequate intake.

Due to the substantial lack of RCTs in this area, further high quality RCTs are required exploring the effects of zinc therapy. In particular there was limited evidence regarding the oral intake of zinc. It is important to note where the studies did address the use of oral zinc, it was in combination with other supplements. Future studies should ensure that only the supplement of zinc is explored in isolation. Furthermore, that the exact dosage, regimen and type of infusion is examined. Additionally, there is a need for further long-term studies in this area. Alongside these single intervention studies, there is also the requirement for combination treatments to explore the synergistic effects of oral zinc supplementation, as zinc is often taken alongside other nutritional supplementation.

CPD reflective questions

1. *What methods of zinc therapy are you aware of for treating pressure sores?*
2. *What are the main methodological limitations of this systematic review?*
3. *What other nutritional factors are you aware of which may influence the healing time of pressure sores?*

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