Review article

A Systematic Review and Meta-Analysis of the effect of Zinc on wound healing

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Abstract: In times of metabolic stress, the demand for nutrients increases, which is essential to prevent delayed healing and development of chronic wounds. This study presents a systematic review and meta-analysis examining the effect of zinc treatment on wound healing. The review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and included data from four electronic data bases. Five clinical trials met the inclusion criteria. The meta-analysis suggested that zinc treatment may be associated with improvements in ulcers healing at the final endpoint MD: 1.41 (95% CI: 1.04, 1.92, p = 0.03). Given the limitations of the included studies, a GRADE assessment indicated a moderate quality of evidence.

Key message: What is already known on this topic: The impact of Zn of healing is known, but there are limited studies studying its effect on wound healing. What this study adds: A previous meta-analysis has been done in 1998 on the effect of Zn on wound healing. The following systematic review and meta-analysis consolidates all the existing evidence and assesses the quality of evidence of the studies added. How this study might affect research, practice or policy: The findings suggest that further research alone or in combination with other treatments are advised considering the ageing population and risks associated with immobility and fragility.

Keywords: Zinc sulfate; zinc oxide, ulcers; inflammation; tissue granulation; re-epithelialization; wound healing

1. Introduction

A wound refers to the physical disruption of functional tissues [1,2]. On the other hand, healing initiates immediately following an injury [2,3], and involves four consecutive stages. These stages are often overlapped and can persist for years [3,4] (Figure 1). The healing process is not always linear, and it can move forward and backwards through the stages due to both extrinsic and intrinsic factors such as cytokines and growth factors, among others. Consequently, numerous interventions, including nutritional strategies [5,6] have been devised to enhance the wound healing process. The role of zinc as an essential micronutrient in the process of wound healing has been the subject of research [7].

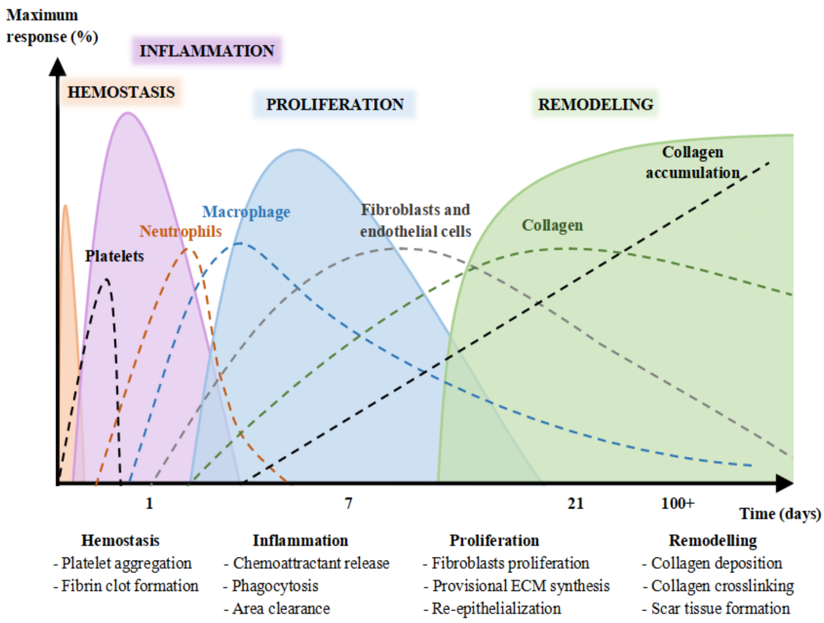

Figure 1. Stages of skin wound healing (haemostasis, inflammation, proliferation, and repair and remodelling) over time. Source: [5].

Description of intervention

Zinc plays a significant role in the physiology of the skin and related appendages [8]. It is present in the human body at less than 50 mg/kg and its usefulness in human health and disease relate to its role in growth and development, wound healing, immune function and the central nervous system [9]. Zinc is the second most abundant mineral in the human body, only after iron [10]. Zinc acts as a cofactor of about 3000 proteins and enzymes in the human genome [11] and as a consequence, it is involved in the function of the nervous system, growth and development [12], bone metabolism, wound healing [13], and immune function [14,15]. It has also been reported that zinc dependent proteins are important in DNA repair, metabolic processing, antioxidant defence and extracellular matrix regulation [9].

Zn deficiency is associated with delayed wound healing [16]. Indeed, critically ill patients in ICU have been reported with low serum Zn levels [17].

However, a well-balanced diet is often sufficient to meet the body's nutritional requirements for zinc of about 8 to 15 mg per day recommended daily allowance for zinc. Diets that are high in protein are often high in zinc, while vegetable diets containing high plant fibre are usually low in absorbable zinc [18].

How the intervention might work

The process of wound healing is intricate and dynamic and includes stages such as haemostasis; inflammation; cell proliferation, re-epithelialisation, granulation and angiogenesis; and remodelling [8,9] (Figure 1). The presence of trace elements such as zinc and other modulators including growth factors and cytokines are important in the wound healing process [8]. These distinct and overlapping phases involve coordination of cytokines and growth factors, endothelial cells and fibroblasts [9]. Zinc has been found to be involved in stimulating re-epithelialisation, decreasing inflammation and the growth of bacteria [8]. Evidence of the effect of zinc in wound repairs can be demonstrated based on the role of zinc metalloenzymes including alkaline phosphatase, RNA and DNA polymerases [18]. Zinc supplementation has also been found to be beneficial in managing ulcer size and promoting metabolic parameters in patients with diabetic foot ulcers [19]. The effect of oral Zinc Sulphate ($ZnSO_4$) on humans with leg or arterial ulcers has been investigated in various studies and gathered in a literature review [20] (Table 2).

Why this Review is Important

Most of the previous reviews in this field have either been mainly narrative reviews [9,18,21,22] or have focused on the role of zinc in the molecular mechanism of wound healing [8,9]. In contrast, the current review is a systematic review and meta-analysis, which should provide a more valid, reliable and robust evidence on the effectiveness of zinc in wound healing.

Aim:

This systematic review and meta-analysis aimed to evaluate the effect of treatment with zinc on wound healing or parameters related to healing.

2. Methods

The following systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [23]. Furthermore, this review follows the Population, Intervention, Comparison, and Outcome (PICO) characterization.

2.1 Search strategy

The following databases were searched for relevant papers from 1950 -2023: Pubmed, Medline, Science Direct and grey literature research with Google Scholar.

Based on the search strategy, the following keywords were searched in "all field" to include title, abstract and text: zinc and (inflammation or healing or wound or surgery or hospital stay). Words were combined using Boolean operators (OR/AND) (Table 1). References from pertinent articles were also examined for additional studies. Searches were conducted and data from the selected articles were extracted by one researcher (EAL) and independently verified by another researcher (NZ). The screening was done by both researchers (EAL and NZ) Differences in the search results and data extracted between the researchers were resolved through discussion. For the meta-analysis data, the authors of the selected articles were contacted for the original data when needed.

Table 1. Search terms and search strategy.

Patient/ Population	Intervention	Outcome	Study Designs	Combining Search Terms
Patients with Ulcers OR Burnt Patients	Zinc	Inflammation OR Healing OR Wound OR Hospital Stay	Clinical trial OR Randomised controlled trial OR controlled clinical trial	Column 1 AND Column 2 AND Column 3 AND Column 4

2.2 Study selection

Inclusion criteria: studies selected were randomised controlled trials (RCTs) and a prospective trial. Patients were above 18 years old in all the studies except for the study carried out by Agren et al. (2006), which also included children. Nevertheless, this study was not included in the meta-analysis. All patients included in the selected studies were suffering from acute or chronic wounds and were treated with zinc (Figure 2). In terms of general health, they were reported to be both healthy and, in some cases, unhealthy.

Exclusion criteria: Studies that did not entail *in vivo* human studies involving treatment with zinc were excluded from the review. Studies involving participants below 18 years of age were excluded from the review due to the metabolic stress already occurring resulting from growth. Studies involving patients with diabetes, where data were not complete or the original data were not presented and studies in another language other than English, Spanish or French were excluded from the review.

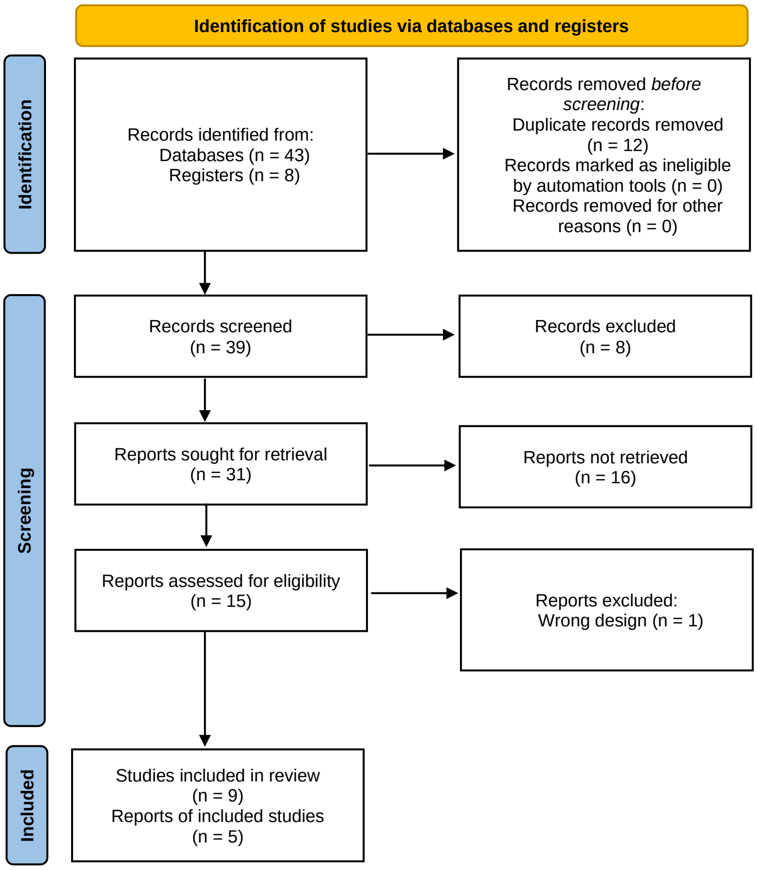

Figure 2. Flow diagram of the search strategy for zinc.

2.2.1 Population

Adults above 18 years old, healthy or unhealthy suffering from acute or chronic wounds.

2.2.2 Intervention

Wounds treated with zinc for up to 12 months.

2.2.3 Comparator

A control group, either treated with a placebo or not treated.

2.2.4 Outcomes

The outcome included in the meta-analysis was the number of healed ulcers at final endpoint.

2.3. Data Extraction and Management

Data for the meta-analysis were extracted from tables and the test from the articles, and the difference in events between the treated and control groups for the outcome were used for the meta-analysis. No publication date restrictions were applied. Median values were converted to means and 1st–3rd quartiles were transformed into standard deviations, respectively. This was done following the method described in the Cochrane Handbook [24], being Mean ≈ Median + [(Q3 − Q1)/2] and SD ≈ (Q3 − Q1)/1.35. These conversions were performed in the Review Manager (RevMan) software, ensuring consistency with Cochrane guidelines for meta-analysis.

2.4. Quality Assessment

The risk of bias assessment was assessed by the Cochrane risk of bias tool [24]. The domains evaluated included the random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Low risk of bias is indicated by a plus (+), unclear risk of bias by a question mark (?), and high risk of bias by a minus (−).

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group [25] was used to assess the quality of evidence of the results obtained from the meta-analysis, including risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias.

2.5. Data Analysis

Changes from baseline for the intervention were compared with the control in all the parameters analysed [24]. The pooling of the data was conducted with the meta-analytic methodology, utilizing Cochrane Review Manager 5.4.1 (2020) [26] for the different outcomes evaluated applying fixed effects, the mean differences (MDs) and risk ratio as a degree of effect extent. Pooled effect size estimates are presented with their 95% confidence intervals (95% CI). Heterogeneity was assessed using I^2 and Chi^2 and considered significant when $I^2 > 50\%$. Results were considered significant when the p-value was below 0.05.

4. Results and discussion

Nine (9) studies on zinc were included in the systematic review (Table 2).

Table 2. Studies evaluating the effect of zinc supplementation on wound healing and reported outcomes.

Study	Duration	Patient population	n	Supplementation	Results
[27] Clayton (1972)	-	Ulcer patients (chronic wound)	10	220 mg $ZnSO_4$*	↑ Healing rate
[28] Greaves and Ive (1972)	4 months	Ulcer patients (chronic wound)	38	3x200 mg $ZnSO_4$*	↑ Healing rate
[29] Haeger, Lanner and Magnusson (1972)	3 months	Ulcer patients (chronic wound)	36	3x200 mg $ZnSO_4$*	↑ Healing rate
[30] Hallböök and Lanner (1972)	4 months	Ulcer patients (chronic wound)	27	3x200 mg $ZnSO_4$*	↑ Healing rate
[31] Haeger and Lanner (1974)	12 months	Ulcer patients (chronic wound)	30	3x200 mg $ZnSO_4$*	↑ Healing rate
[32] Phillips, Maureen and Greaves (1977)	10 months	Ulcer patients (chronic wound)	42	2x220 mg $ZnSO_4$*	↑ Healing rate
[33] Strömberg and Ågren (1984)	8 weeks	Elderly ulcer patients (chronic wound)	37	400 µg/cm2 of ZnO**	↑ Healing rate ↓ Ulcer area
[34] Gang (1981)	5 months	Deep burn patients (acute wound)	40	40% ZnO**	↑ Healing rate
[35] Ågren et al. (2006)	Up to 82 days	Open wounds patients (acute wound)	64	3% ZnO**	↑ Healing rate

ZnO: Zinc Oxide; $ZnSO_4$: Zinc Sulphate; ↑: Increased; ↓ Decreased; *: Per Os; **: Topical.

3.1 Risk of Bias of Included Studies on Zinc

The risks of bias in the included studies are illustrated in Figure 3. Based on random sequence generation, only Gang (1991) showed a high risk of bias, while the rest were assessed as having either low or unclear risk. All the studies have demonstrated a low or an unclear risk of bias regarding allocation concealment, except Phillips et al. (1977) and Gang (1981), which exhibited a high risk of bias. Likewise, all the studies have demonstrated a low or an unclear risk of bias regarding incomplete outcome data, except Haeger et al. (1972, 1974) which showed a high risk of bias. With respect to blinding of participants and blinding of outcome, all the studies have demonstrated a low or an unclear risk of bias. Most of the studies showed a low risk of bias in terms of selective reporting, while three of them showed high risk [28,29,31]. Three studies were judged at high risk of bias due to baseline imbalance in the mean ulcer area with no clarification if this was adjusted when doing the analysis [27,29,31].

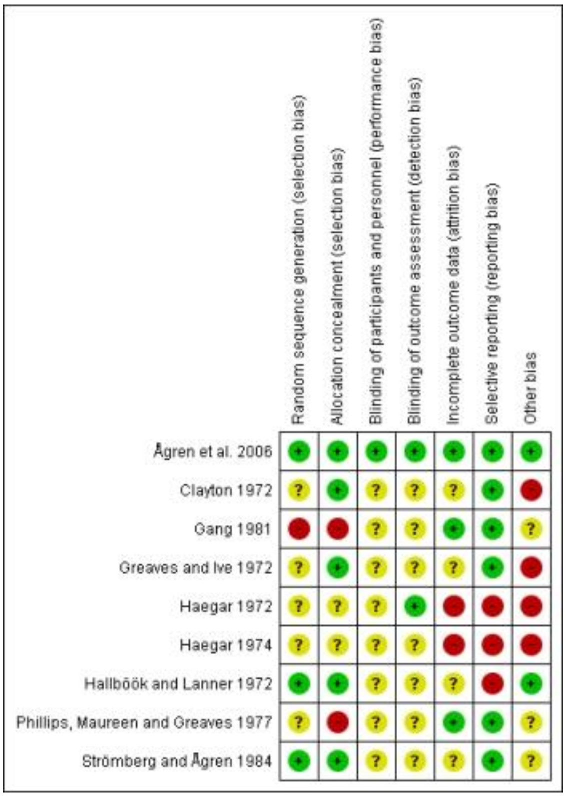

Figure 3. Risk of bias summary for the included studies on zinc. Low risk of bias (+), unclear risk of bias (?), and high risk of bias (−).

A3.2. Effects of Interventions

Based on the systematic review and meta-analysis, a distinct area was identified under zinc: ulcers healed at final endpoint. 3 studies did not measure this parameter and hence were not included in the meta-analysis [27,31,34].

Research on the pharmacological effects of zinc treatment has been mostly based on its use for chronic wounds, although some trials have studied its effect on acute wounds (Table 2).

Clayton (1972) [27] conducted a double-blind RCT on 10 patients supplemented with either 220 mg of $ZnSO_4$ or lactose as a placebo. The frequency and duration of the treatment were not recorded, although there was a 4-week follow-up. They measured the average of 90% healing rate, being 13.5 days greater for the treated group (25.5 days) than for controls (12.0 days) (no range given). However, the average ulcer side was 47% larger in the control group, most likely attributing a detrimental effect on wound healing. Given this information, not much can be inferred from these results.

Greaves and Ive (1972) [28] performed a similar double-blind RCT, where patients were treated with either 200 mg of $ZnSO_4$ or lactose, 3 times a day until ulcers were healed, with 4 months follow-up. It was reported that those in the study group were 1.3 times more likely to have their ulcers healed at 4 months (95% CI, 0.28 - 7.95). However, according to the author, the results from the mean healing rate were skewed and, thus, not reliable. This could explain the broad range of the confidence interval seen in this systemic review, hence affecting the overall effect in the meta-analysis.

Similar results were reported by Haeger et al. (1972, 1974) [29,31] in two other double-blind RCTs on patients under similar conditions as the latter trial, but using an unidentified placebo. The supplemented group in these RCTs were seen to be more likely to heal their ulcers within the three months (95% CI, 0.84 - 2.33) or one year of treatment compared to the control group.

Hallböök and Lanner (1972) [30] also supplemented 200 mg of $ZnSO_4$ or an unspecified placebo, 3 times per day for 4 months in a double-blind RCT on 27 patients. They observed that the healing process in the intervention group (9/13) was 1.5 times faster than in the control group (8/14) (95% CI, 0.67 - 2.31). However, on examining the baseline, Zn serum levels in both study groups, patients with serum levels lower than 16.8 μmol/L, had their wounds healed 5 times faster than the respective patients in the placebo group (5/7 vs. 1/7) (95% CI 0.77 - 32.5). Meanwhile, when the serum Zn levels of the patients were equal to or higher than 16.8 μmol/L, those in the control group experienced 0.67 times faster healing (7/7 vs. 4/6) (95% CI, 0.84 - 2.33). Moreover, it was mentioned that the mean ulcer size in the study group was 74% larger than in the control group, which could have influenced the outcome. It is also important to note that, due to the great difference in the size of the ulcer and their irregular behaviour, only ulcers between 100 and 1000 mm^2 were taken into account for the statistics analysis in their trial.

Phillips, Maureen and Greaves (1977) [32] conducted a double-blind RCS on 42 patients, supplemented with 220 mg of $ZnSO_4$ twice per day until their ulcers healed for 10 months. Similar to the findings in the previous trials, the Zn-supplemented group healed 1.01 times faster than controls (95% CI, 0.57 – 1.80) at 10 months (10/19 vs. 12/23).

Unlike the previous trials, Strömberg and Ågren (1984) [33] used ZnO instead of $ZnSO_4$ to determine the effect of ZnO on leg ulcers. In this double-blind RCT, 37 elderly patients were topically treated with 400 $\mu g/cm^2$ of ZnO for 8 weeks. On completion of the trial, the study group presented an 83% success rate compared to the group given a placebo (unknown), with a 42% success rate ($p < 0.05$), calculated by the measurement of the ulcer size and debridement, and the existence or lack of granulation tissue. The median ulcer area in the Zn group decreased from 4.2 cm^2 (1.4 – 85.4 cm^2) to 2.7 cm^2 (0 – 65.0 cm^2), while the placebo group was reduced from 3.6 cm^2 (0.5 - 14.4 cm^2) to 0.4 (0 - 17.1 cm^2). Six patients in each group suffered from diabetes which might have slightly influenced the results.

Gang (1981) [34] investigated the effect of topical 40% ZnO, through an adhesive tape, on 40 patients with deep burnt injuries (5 - 20%) for 5 months. While half of the patients were treated with adhesive tape, the other half were treated by the exposure method, where no tape was applied. The study group had their wounds healed in the meantime of 9 days compared to the non-treated group, which needed about 12 days. In addition, it was also noted that in the treated group, there was a better separation of the necrotic eschar in the burns, thus exposing, the surface of the granulation tissue without traumatizing viable tissue. Nevertheless, this trial was controlled but not blinded, and it is not mentioned if was randomized; therefore, the outcome could be biased. In addition, children were also assessed in this study which could influence the outcome due to the metabolic stress already occurring resulting from growth.

Ågren et al. (2006) [35] also studied the effect of topical ZnO on 64 patients (53 men) with open wounds in a double-blind, multicentre RCT. In this trial, patients treated with 3% topical ZnO showed a reduced median healing time of 54 days (42 - 71 days), while the control group, the placebo group, treated with PVP, needed a median of 62 days (55 - 82 days) ($p = 0.32$). Moreover, only 3 patients from the ZnO were required to be prescribed antibiotics, while in the control group, 12 needed a prescription ($p < 0.05$). This study not only proved the potential of this compound to promote wound healing but also to reduce infections.

This review included nine studies, of which five were incorporated into the meta-analysis, involving a total of 178 participants to assess the effectiveness of zinc treatment on chronic ulcer healing rates (Figure 4). The analysis suggested a statistically significant overall effect, with a risk ratio of 1.41 (95% CI: 1.04–1.92; $p = 0.03$). This indicates that patients supplemented with zinc had a 41% higher likelihood of experiencing favourable healing outcomes compared to those who did not receive the intervention. The I^2 statistic was 0, indicating low heterogeneity among the studies.

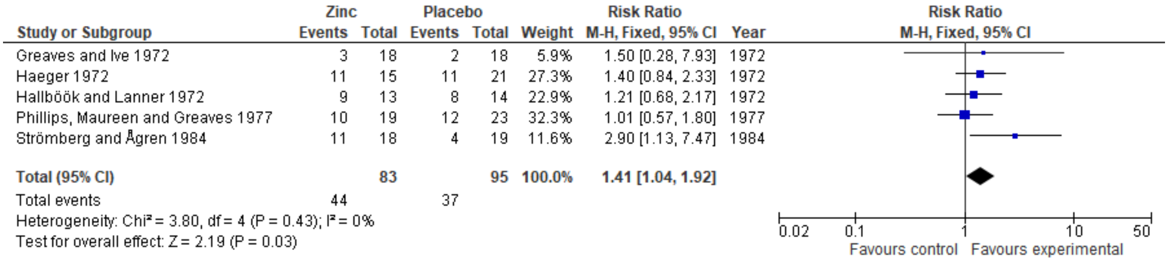

Figure 4. Ulcers healed at final endpoint: fixed-effects meta-analysis and forest plot from studies providing treatment of zinc.

However, after evaluating the quality of the evidence following GRADE, the quality of evidence was found to be moderate, indicating further research is likely to affect confidence in the estimated effect (Table 3). It is important to note that the studies included in the review are relatively old and of suboptimal quality, as evidenced by the small number of participants across all studies. These factors were considered when assessing the quality of evidence, leading to its downgrading, along with the moderate risk of bias in some studies.

Table 3. GRADE evidence profile (EP) for the 5 studies included in the meta-analysis review - Quality assessment of evidence

Ulcers healing rate

Patient or population: patients with chronic ulcers
Settings: randomized clinical trial
Intervention: treatment with Zinc
Comparison: usual care

Outcome	Risk Ratio (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Ulcers healed at final endpoint	1.4 (1.04, 1.92)	178 (5)	⊕⊕◯◯ MODERATE	Low imprecision and low risk of bias in some the of studies

Discussion

Based on the results of this systematic review and meta-analysis, that treatment with zinc might be effective in promotion of wound healing ($p < 0.05$). These findings are in accordance the results of previous systematic review and meta-analysis which also showed that zinc therapy can promote wound healing, and the authors recommended that medical staff should consider providing patients with zinc during treatment of pressure injuries [22]. However, Wilkinson and Hawke (1998) [36] found that the benefit of the use of zinc sulphate in patients with chronic leg ulcers were not statistically significant and thus recommended the need for further research to evaluate the effect of oral zinc sulphate in managing patients with leg ulcers. The difference between the present review and the review by Wilkinson and Hawke (1998) [36] is that, the present review included zinc sulphate and zinc oxide, whilst the Wilkinson and Hawke (1998) had only zinc sulphate in the studies included.

There are two forms of Zinc supplementation (ZnO and $ZnSO_4$) reported in the literature, which have been administered, topically, intraperitoneally, and orally.

ZnO has been shown to enhance the immune system and wound healing, especially the inflammatory phase, regardless of its form of delivery [33,35] as seen with the healing of ulcers [36].

On the other hand, $ZnSO_4$ has been suggested to inhibit epithelial effect possibly due to its local toxic effects on wounds [37]. This could be explained by their difference in solubility between of $ZnSO_4$, and ZnO. ZnO solubility allows it to maintain a sustained release of bioavailable Zn in the wound site [38,39]. Therefore, form, dose and route of delivery should be considered to achieve a better effect of Zn supplementation in wound healing.

In particular, it should be noted that prolonged intake of high dose Zn supplementation (40 mg/day), could inhibit the absorption and ultimately bioavailability of copper causing Zinc-induced copper deficiency (ZICD). ZICD is known to cause further clinical issues including anaemia and neutropenia, since copper is a critical coenzyme in a number of cellular processes [40].

Limitations of the Review

Although nine studies were included in the systematic review, only five met the eligibility criteria for inclusion in the meta-analysis. To account for the limitations related to the age of time elapsed since the study was conducted the studies, small sample sizes, and the overall limited number of studies, a GRADE assessment was performed. As a result, the quality of the evidence was downgraded to moderate. Consequently, the findings of this review should be interpreted with caution.

4. Conclusions

Zn is needed as a cofactor for many enzymes in the human body, and due to its role in functions, its deficiency can delay wound healing [18,21].

There is evidence that the healing of wound, inflammation and immune response are closely related, and it has been demonstrated that zinc is capable of modulating both innate and adaptive immune functions [9]. The alteration of immune responses by zinc is often through a range of methods including inflammatory signalling, myeloid-derived cells, lymphocyte differentiation and antibody production [9]. Furthermore, topic zinc has been reported to decrease inflammation and bacterial growth, while stimulating re-epithelialization [8].

Based on this systematic review, Zinc treatment could promote wound healing compared to control ($p = 0.03$). However, due to the moderate quality of the included studies, as determined by the GRADE assessment, these findings should be interpreted with caution. Further studies including randomised controlled trials are needed to fully examine the effects of Zn on wound healing.

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Ethics declaration: All methods used in this research comply with relevant guidelines and regulations.

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