Evidence-Based Nutritional Interventions in Wound Care

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Background: The role of nutritional intervention in wound care has been a topic of controversy. Although the efficacy of macronutrient supplementation has been well described, there is a paucity of evidence and no official recommendation regarding the use of vitamins and minerals to optimize wound healing. This is the first review of vitamin and mineral wound intervention that systematically summarizes the literature using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and distills the evidence by wound type.
Methods: In this comprehensive review, the authors outline the nutrients and delivery methods used in the identified studies, analyze reported treatment outcomes, summarize nutrient effectiveness, and propose evidence-based conclusions to improve wound healing outcomes and enhance the consistency of nutritional intervention in wound care.
Results: Thirty-six studies with a combined total of 2339 patients investigated the use of oral, topical, or intravenous vitamin and/or mineral supplementation for treatment of the following wound types: burn wounds ($n = 3$), pressure ulcers ($n = 7$), diabetic ulcers ($n = 4$), venous ulcers ($n = 7$), digital ulcers ($n = 1$), skin incisions ($n = 9$), hypertrophic scars ($n = 4$), and sinonasal wounds ($n = 1$). Improved outcomes were reported in patients with burn wounds receiving vitamins A, B_1, B_6, B_{12}, D, and E and zinc, calcium, copper, magnesium, selenium, and zinc; patients with pressure ulcers receiving vitamin C and zinc; patients with diabetic ulcers receiving vitamin A, B_9, D, and E; patients with venous ulcers receiving zinc; and patients with hypertrophic scars receiving vitamin E.
Conclusions: Based on the high-level data provided in this review, the use of specific nutritional interventions may improve the outcome of certain wound types. Further investigation is warranted to draw definitive conclusions. (*Plast. Reconstr. Surg.* 148: 226, 2021.)

Adequate nutrition is essential for proper wound healing. Despite numerous studies, the use of nutritional intervention to enhance wound healing remains controversial. Although the efficacy of macronutrients such as carbohydrates, proteins, and fats has been well described, there is little evidence and no official recommendation from any health care organization regarding micronutrient supplementation for optimal wound care.

This review will investigate the evidence to support wound-specific nutritional interventions to improve treatment outcomes and reduce complication rates. The four specific objectives of this review are to (1) conduct a comprehensive search of the published literature on nutritional interventions in wound healing, (2) outline the nutrients used in the identified studies, (3) analyze outcomes, and (4) propose evidence-based guidelines.

PATIENTS AND METHODS

For a high standard of reporting, procedures indicated by the Preferred Reporting Items for

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Systematic Reviews and Meta-Analyses guidelines were followed.

Literature Search

The PubMed and Embase databases were searched on July 11, 2020, for all English-language publications containing the following terms: "wound healing" AND "vitamins" OR "nutrients." (**See Appendix, Supplemental Digital Content 1**, which shows the search strategy and Medical Subject Heading terms, ***http://links.lww.com/PRS/E505***.)

Selection Criteria

Publications that met the following criteria were included: randomized controlled trials, prospective studies, and retrospective studies with at least 20 subjects. We excluded nonhuman studies, case reports, case series, reviews, letters, commentaries, and studies lacking nutritional intervention, wound outcomes, or a control group, to maintain a high level of evidence. The most common reasons for exclusion were wrong study design or publication type and studies with wrong or no intervention. This search was supplemented by a reference list review for potentially eligible studies. Three reviewers independently screened and extracted data in two steps: (1) titles and abstracts, and (2) full-text articles.

Outcomes

Our primary outcome of interest was time to definitive wound closure with nutrient supplementation. Our secondary outcome of interest was the incidence of wound complications.

Data Extraction

A standardized data abstraction form recorded the following information regarding each relevant study: (1) article author, (2) study design, (3) level of evidence, (4) number of patients, (5) nutrient evaluated, (6) delivery method evaluated, and (7) study outcomes.

RESULTS

Study Selection

The identification, screening, eligibility, and inclusion processes are demonstrated in Figure 1. We initially identified 641 publications. After duplicates were removed, 597 articles were screened based on title and abstract. Three-hundred sixteen articles were irrelevant. Full-text review and application of our inclusion criteria to the remaining 281 publications produced 36 relevant studies with a total of 2339 patients undergoing nutritional intervention during wound care.

Description of Included Studies

Among the 36 included studies, there are three studies with a total of 114 patients receiving treatment for burn wounds, seven studies with 451 patients receiving treatment for pressure ulcer wounds, four studies with 170 patients receiving treatment for diabetic ulcer wounds, seven studies with 421 patients receiving treatment for venous ulcer wounds, one study with 27 patients receiving treatment for digital ulcers, nine studies with 864 patients receiving treatment for skin incision wounds, four studies with 262 patients receiving treatment for hypertrophic scars, and one study with 30 patients receiving treatment for sinonasal wounds (Table 1).[1–36] A summary of effectiveness is provided in Table 2, and a histogram overview of outcomes is provided in Table 3.

Burn Wounds

Vitamins A, B_1, B_6, B_{12}, C, D, and E with Calcium and Magnesium

Chen et al. performed a retrospective cohort study (**Level of Evidence III**) with 61 patients receiving vitamin and mineral supplementation along with treatment for major burn injuries greater than or equal to 20 percent of the total body surface area. The authors reported a significant reduction in the length of hospitalization (51.8 days versus 76.8 days; $p = 0.025$), incidence of wound infection (30.0 percent versus 77.4 percent; $p < 0.001$), and sepsis (13.3 percent versus 41.9 percent; $p = 0.021$) in patients receiving daily oral vitamins A, B_1, B_6, B_{12}, C, D, and E, combined with an infusion of 2% calcium chloride and an injection of 10% magnesium sulfate.[1]

Vitamins C and E with Zinc

Barbosa et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence II**) with 32 pediatric burn patients receiving oral vitamin C, vitamin E, and zinc supplementation. The authors reported significantly reduced time to definitive wound closure in the supplementation group compared with the placebo group (5.3 days versus 7.5 days; $p < 0.001$).[2]

Copper, Selenium, and Zinc

Berger et al. performed a prospective, randomized, single-blind, placebo-controlled trial (**Level of Evidence II**) with 21 patients receiving treatment for burn wounds covering total body surface area greater than or equal to 45

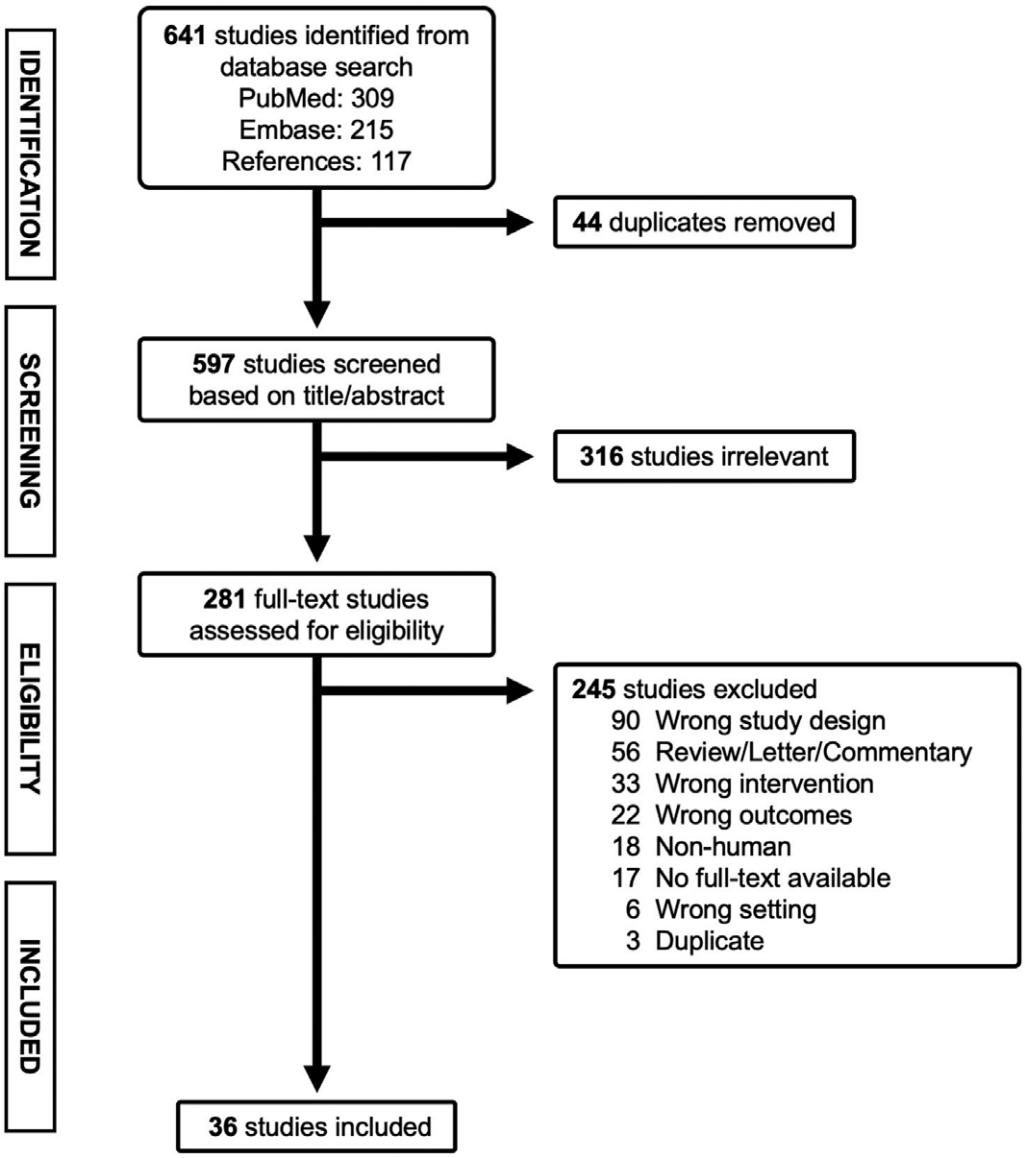


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram describing the screening and selection process for included studies.

percent and intravenous supplementation with copper, selenium, and zinc. The authors reported a reduced incidence of infection (23 episodes versus 36 episodes; $p = 0.015$) and lower requirements for regrafting (94 percent versus 144 percent of total body surface area burned; $p = 0.02$) in the supplementation group compared with the placebo group.[3] A summary of these results is provided in Table 4.

Pressure Ulcer Wounds

Vitamins A, B_9 (Folic Acid), C, and E with Zinc, Selenium, and Copper

Van Anholt et al. performed a multicountry, randomized, double-blind, controlled trial (**Level of Evidence I**) with 43 nonmalnourished patients receiving treatment for stage III or IV pressure ulcers. Patients were given 200 ml of an oral nutritional supplement consisting of 1.5 mg of vitamin A, 200 mg of vitamin B_9 (folic acid), 250 mg of vitamin C, 38 mg of vitamin E, 9 mg of zinc, 64 mg of selenium, and 1.35 mg of copper or a noncaloric control product three times per day for 8 weeks in addition to standard wound care. The authors reported significant decreases in mean ulcer size ($p < 0.016$) and Pressure Ulcer Scale for Healing severity scores ($p < 0.033$), fewer dressing changes ($p < 0.045$), and shorter operative times ($p < 0.022$) in the supplementation group compared with the control group.[4] In

Table 1. Summary of Articles

Reference	Study Type	LOE	No. of Patients	Nutrient(s) Evaluated	Delivery Method(s) Evaluated	Study Outcome
Burn wounds						
Chen et al., 2018[1]	Retrospective	III	61	Vitamins A, B_1, B_6, $B1_2$, C, D, E; calcium; magnesium	Oral, parenteral	Significant reduction in the length of hospitalization (51.8 vs. 76.8 days; $p = 0.025$), incidence of wound infection (30.0% vs. 77.4%; $p < 0.001$), and sepsis (13.3% vs. 41.9%; $p = 0.021$)
Barbosa et al., 2009[2]	RCT	II	32	Vitamins C and E; zinc	Oral	Time to definitive wound closure was significantly reduced in the supplementation group (5.3 days vs. 7.5 days; $p < 0.001$)
Berger et al., 2007[3]	RCT	II	21	Copper, selenium, zinc	Parenteral	Supplementation reduced the incidence of infection (23 episodes vs. 36 episodes; $p = 0.015$) and the requirement for regrafting (94% vs. 144% of TBSA burned, $p = 0.02$)
Pressure ulcer wounds						
van Anholt et al., 2010[4]	RCT	I	43	Vitamins A, B_9, C, E; copper, selenium, zinc	Oral	Significant reduction in mean ulcer size ($p < 0.016$), PUSH scores ($p < 0.033$), fewer dressing changes ($p < 0.045$), and shorter operative times ($p < 0.022$) compared with placebo
Theilla et al., 2007[5]	RCT	II	100	Vitamins A, C, E	Oral	Supplementation had no significant effect on existing ulcers but significantly reduced the incidence of new pressure ulcers ($p < 0.05$)
Forrest et al., 1980[6]	RCT	II	20	Vitamin C	Oral	Supplementation reduced pressure ulcer surface area by 84% compared with 42.7% in the placebo group ($p < 0.005$)
ter Riet et al., 1995[7]	RCT	I	88	Vitamin C	Oral	Supplementation did not significantly reduce overall time to definitive wound closure ($p = 0.82$)
Soriano, 2004[8]	Prospective	II	69	Vitamin C; zinc	Oral	3 wk of supplementation significantly reduced median wound area (19.2 cm^2 vs. 23.6 cm^2; $p < 0.001$) compared with control
Cereda et al., 2009[9]	RCT	II	28	Vitamin C; zinc	Oral	Supplementation significantly reduced pressure ulcer surface area at 8-wk follow-up (57% vs. 33%; $p < 0.02$) and PUSH scores (−6.1 vs. −3.3; $p < 0.05$) vs. control
Houwing et al., 2003[10]	RCT	I	103	Zinc	Oral	Zinc supplementation may delay onset but did not significantly reduce incidence rate versus control group ($p < 0.09$)
Diabetic ulcer wounds						
Tom et al., 2005[11]	RCT	II	24	Vitamin A	Topical ointment	Significantly decreased ulcer surface area (−54.7 ± 28.8% vs. +2.7 ± 47.2%; $p < 0.01$) and depth (−60.1 ± 13.8% vs. −29.6 ± 12.6%; $p < 0.02$) after 16 wk of topical tretinoin therapy compared with placebo
Boykin et al., 2020[12]	Retrospective	III	29	Vitamin B_9	Oral	Significant decrease in DFU wound area after oral supplementation with 5 mg of vitamin B_9 (folic acid) daily for 4 wk (−5.6 cm^2 vs. −0.1 cm^2; $p < 0.05$) compared with control
Razzaghi et al., 2017[13]	RCT	I	60	Vitamin D	Oral	Significant reduction in ulcer length (−2.1 cm vs. −1.1 cm; $p = 0.001$), width (−2.0 cm vs. −1.1 cm; $p = 0.02$), depth (−1.0 cm vs. −0.5 cm; $p < 0.001$), and erythema rate (100% vs. 80%; $p = 0.01$) in patients receiving vitamin D supplementation vs. placebo
Afzali et al., 2019[14]	RCT	I	57	Vitamin E; magnesium	Oral	Significant reduction in ulcer length (−1.2 cm vs. −0.8 cm; $p = 0.003$), width (−0.9 cm vs. −0.7 cm; $p = 0.02$), and depth (−0.5 cm vs. −0.2 cm; $p = 0.02$) in the supplementation group compared with placebo
Venous ulcer wounds						
de Franciscis et al., 2015[15]	Prospective	II	87	Vitamin B_9 (folic acid)	Oral	Rate of total ulcer area reduction per week (−1.1 cm^2 vs. −0.92 cm^2; $p < 0.05$) and the rate of definitive wound closure (78.8% vs. 63.3%; $p < 0.05$) significantly improved compared with control
Burkiewicz et al., 2012[16]	Prospective	II	52	Vitamin D	Oral	8 wk of vitamin D supplementation did not significantly improve wound healing or ulcer size compared with the placebo group ($p = 0.79$)
Lee, 1953[17]	RCT	I	57	Vitamin E	Oral	Oral vitamin E supplementation did not significantly improve wound healing or reduce ulcer size compared with placebo group ($p = 0.7$)
Strömberg and Agren, 1984[18]	RCT	II	37	Zinc	Topical adhesive dressing	Significant reduction in wound size with topical zinc dressing vs. placebo ($p < 0.05$)

(*Continued*)

Table 1. *Continued*

Reference	Study Type	LOE	No. of Patients	Nutrient(s) Evaluated	Delivery Method(s) Evaluated	Study Outcome
Eriksson, 1986[19]	RCT	II	34	Zinc	Topical adhesive dressing	No significant differences in ulcer size or volume after 12 wk of treatment with topical zinc dressing vs. placebo
Hallböök and Lanner, 1972[20]	RCT	I	50	Zinc	Oral	Significantly shorter time to definitive wound closure in patients with serum zinc concentrations above 110 μg/dl or after receiving oral supplementation with 200 mg zinc sulfate three times daily for 18 wk ($p < 0.01$)
Husain, 1969[21]	RCT	I	104	Zinc	Oral	Significantly shorter time to definitive wound closure in patients receiving oral zinc supplementation vs. placebo ($p < 0.001$)
Digital ulcer wounds						
Fiori et al., 2009[22]	RCT	II	27	Vitamin E	Topical gel	Significant reduction in time to definitive wound closure with topical vitamin E gel vs. placebo ($p < 0.001$)
Skin incision wounds						
Tan and Tope, 2004[23]	Prospective	II	29	Vitamin A	Oral	No significant differences in the rates of infection, dehiscence, and hypertrophic scarring compared with control group
Odgaard et al., 2019[24]	RCT	I	79	Vitamin C; zinc	Oral	Patients reported improved pain ($p = 0.21$), pruritus ($p = 0.026$), and satisfaction with scar cosmesis ($p = 0.033$) but no significant differences in scar vascularity, pigmentation, thickness, relief, pliability, or surface area vs. control group
Yun et al., 2013[25]	RCT	I	80	Vitamin C	Topical gel	Significant decrease in scar elevation ($p = 0.026$), erythema ($p = 0.025$), and melanin index ($p = 0.045$) compared with nontreated group at 6-mo follow-up
Zampieri et al., 2010[26]	RCT	I	428	Vitamin E	Topical gel	Lower incidence of keloid formation (0% vs. 6.5%; $p < 0.05$) and higher patient satisfaction with cosmesis (96% vs. 78%, $p < 0.05$) at 6-mo follow-up vs. placebo
Stanizzi et al., 2017[27]	RCT	I	60	Vitamin E	Topical adhesive dressing	No significant differences in outcomes or time to wound closure in treatment group vs. placebo
Pazyar et al., 2019[28]	RCT	I	63	Vitamin K	Topical ointment	No significant difference in time to definitive wound closure (10.6 days vs. 12.4 days; $p = 0.6$) in patients receiving topical vitamin K compared with placebo
Pories et al., 1967[29]	RCT	II	20	Zinc	Oral	43% shorter time to definitive wound closure with oral zinc supplementation vs. control ($p < 0.01$)
Barcia, 1970[30]	RCT	II	20	Zinc	Oral	No significant differences in granulation tissue production or time to wound closure
Pastorfide et al., 1989[31]	RCT	I	85	Magnesium, zinc	Topical spray and ointment	Improved rate of definitive wound closure by postoperative day 4 (68.8% vs. 37.8%; $p < 0.05$), reduced rate of infection (6.3% vs. 18.9%; $p < 0.05$), and reduced rate of dehiscence (0% vs. 8.1%; $p < 0.05$) with supplementation vs. placebo
Hypertrophic scars						
van der Veer et al., 2009[32]	RCT	II	30	Vitamin D	Topical ointment	No significant difference in the incidence of hypertrophic scar formation between vitamin D–treated scars and placebo
Palmieri et al., 1995[33]	RCT	I	80	Vitamin E	Topical silicone strips	Topical silicone sheets with vitamin E significantly improved scar appearance vs. silicone sheets alone at 8-wk follow-up ($p < 0.05$)
Perez et al., 2010[34]	RCT	II	30	Vitamin E	Topical gel	Improved scar appearance ($p < 0.01$) with reduction in scar volume ($p = 0.01$), length ($p = 0.02$), induration ($p < 0.01$), erythema ($p < 0.01$), and pigmentation alteration ($p < 0.01$) compared to placebo group
Khoo et al., 2011[35]	RCT	I	122	Vitamin E	Topical ointment	Topical vitamin E applied twice-daily for 6 wk did not improve the appearance, vascularity, or incidence of hypertrophic scar formation at 4-mo follow-up
Sinonasal wounds						
Fang et al., 2015[36]	RCT	II	30	Vitamin A	Topical ointment	Significantly lower LK scores for scar and adhesion formation (0.23 vs. 0.53; $p < 0.05$) and significantly larger mean antrostomy size (0.70 cm^2 vs. 0.57 cm^2; $p < 0.01$) at 12-mo follow-up

LOE, level of evidence; TBSA, total body surface area; RCT, randomized controlled trial; PUSH, Pressure Ulcer Scale for Healing; DFU, diabetic foot ulcer; LK, Lund-Kennedy.

Table 2. Summary of Effectiveness*

NUTRIENT	WOUND TYPE (No. of Studies)							
	Burn (3)	Pressure Ulcer (7)	Diabetic Ulcer (4)	Venous Ulcer (7)	Digital Ulcer (1)	Skin Incision (9)	Hypertrophic Scar (4)	Sinonasal (1)
Topical								
Vitamin A			•					•
Vitamin C						•		
Vitamin D							o	
Vitamin E					•	• o	• • o	
Vitamin K						o		
Magnesium						•		
Zinc				• o		•		
Oral								
Vitamin A	•	• o				o		
Vitamin B1	•							
Vitamin B6	•							
Vitamin B9		•	•	•				
Vitamin B12	•							
Vitamin C	• •	• • • • o o				o		
Vitamin D	•		•	o				
Vitamin E	• •	• o	•	o				
Copper		•						
Magnesium			•					
Selenium		•						
Zinc	•	• • • o		• •		• o o		
Parenteral								
Calcium	•							
Copper	•							
Magnesium	•							
Selenium	•							
Zinc	•							

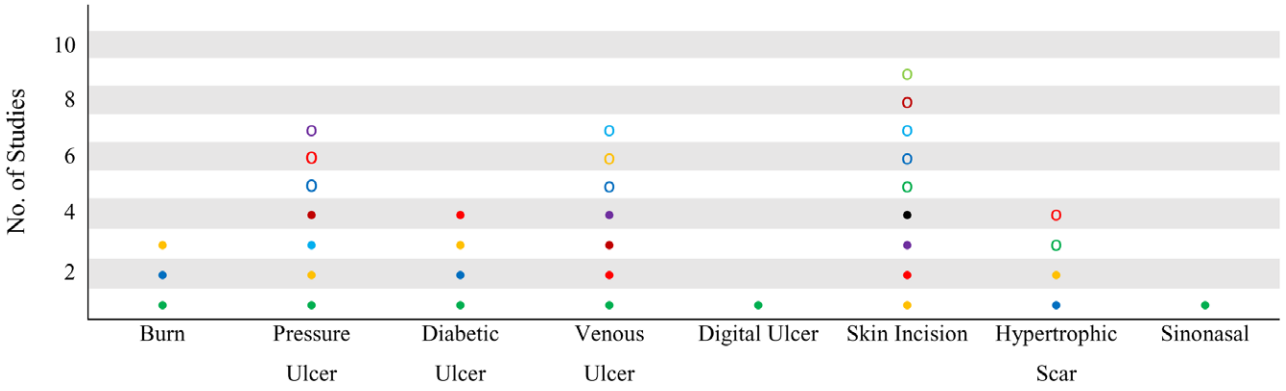
**Closed circle* (•) denotes a significant wound improvement reported with nutrient supplementation. *Open circle* (o) denotes no significant wound improvement reported with nutrient supplementation. Color symbols are defined as follows: burn: •[1] •[2] •[3]; pressure ulcer: •[4] o[5] •[6] o[7] •[8] •[9] o[10]; diabetic ulcer: •[11] •[12] •[13] •[14]; venous ulcer: •[15] o[16] o[17] •[18] o[19] •[20] •[21]; digital ulcer: •[22]; skin incision: o[23] o[24] •[25] •[26] o[27] o[28] •[29] o[30] •[31]; hypertrophic scar: o[32] •[33] •[34] o[35]; sinonasal: •[36].

contrast, a randomized, open-label, controlled trial (**Level of Evidence II**) performed by Theilla et al. found no significant effect on existing pressure ulcers with oral vitamin A, C, and E supplementation. However, the authors reported a significantly decreased incidence of new pressure ulcers in the supplementation group ($p < 0.05$).[5]

Vitamin C

Taylor et al. investigated the utility of vitamin C supplementation for treatment of pressure ulcer

Table 3. Histogram Overview: Outcomes of Nutritional Intervention on Wound Healing*



Closed circle (•) denotes a significant wound improvement reported with nutrient supplementation. *Open circle* (○) denotes no significant wound improvement reported with nutrient supplementation. Color symbols are defined as follows: burn: •[1] •[2] •[3]; pressure ulcer: •[4] ○[5] •[6] ○[7] •[8] •[9] ○[10]; diabetic ulcer: •[11] •[12] •[13] •[14]; venous ulcer: •[15] ○[16] ○[17] •[18] ○[19] •[20] •[21]; digital ulcer: •[22]; skin incision: ○[23] ○[24] •[25] •[26] ○[27] ○[28] •[29] ○[30] •[31]; hypertrophic scar: ○[32] •[33] •[34] ○[35]; sinonasal: •[36].

wounds in a randomized controlled trial (**Level of Evidence II**) with 20 patients. The authors reported a reduction in pressure ulcer surface area of 84 percent after 1 month of oral vitamin C supplementation compared to 42.7 percent in the placebo group ($p < 0.005$).[6] However, ter Riet et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) with 88 patients undergoing treatment for pressure ulcers with vitamin C supplementation and found that supplementation did not decrease the time to definitive wound closure ($p = 0.82$).[7]

Vitamin C with Zinc

Soriano performed a prospective, open-label, controlled trial (**Level of Evidence II**) with 69 patients receiving oral vitamin C and zinc supplementation for treatment of pressure ulcer wounds. The authors reported significantly reduced median wound areas (19.2 cm^2 versus 23.6 cm^2; $p < 0.001$) after 3 weeks of supplementation compared with control.[8] In addition, Cereda et al. performed a randomized, double-blind, controlled trial (**Level of Evidence II**) with 28 patients receiving 400-ml oral vitamin C and zinc supplementation for treatment of pressure ulcers. The authors reported a significant reduction in pressure ulcer surface area at 8-week follow up (57 percent versus 33 percent; $p < 0.02$) and Pressure Ulcer Scale for Healing scores (−6.1 versus −3.3; $p < 0.05$) in the supplementation group compared with the control group.[9]

Zinc

Houwing et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) with 103 patients receiving zinc supplementation along with treatment for pressure ulcers. The authors concluded that zinc supplementation may delay the onset of new pressure ulcers but does not significantly reduce the incidence rate ($p = 0.09$).[10] A summary of these results is provided in Table 5.

Diabetic Ulcer Wounds

Vitamin A

Tom et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence II**) with 24 patients with diabetic foot ulcer wounds

Table 4. Summary of Results for Burn Wounds

Three studies (**Level of Evidence II and III**) provided appropriate data for analysis, 114 patients with burn wounds underwent nutritional intervention with vitamins A, B_1, B_6, B_{12}, C, D, E, and calcium, copper, magnesium, selenium, and zinc. Our review demonstrated:

- Reduced length of hospitalization with oral vitamins A, B_1, B_6, B_{12}, C, D, and E, and parenteral calcium and magnesium supplementation
- Reduced time to definitive wound closure with oral vitamins C and E and zinc supplementation
- Reduced incidence of infection and sepsis with parenteral copper, selenium, and zinc supplementation
- Reduced requirement for regrafting with parenteral copper, selenium, and zinc supplementation

Table 5. Summary of Results for Pressure Ulcer Wounds

Seven studies (**Level of Evidence I and II**) provided appropriate data for analysis; 451 patients with pressure ulcer wounds underwent nutritional intervention with vitamins A, B_9, C, and E; and copper, selenium, and zinc. Our review demonstrated:

- Reduced total ulcer surface area, PUSH scores, total dressing changes, and operative times with oral vitamins A, B_9, C, and E, and copper, selenium, and zinc supplementation
- Reduced total ulcer surface area and PUSH scores with oral vitamin C and zinc supplementation
- However, the data are heterogenous (one study reported no effect with vitamins A, C, and E; one study reported no effect with vitamin C; and one study reported no effect with zinc)

PUSH, Pressure Ulcer Scale for Healing.

receiving topical tretinoin (vitamin A derivative) cream therapy daily for 4 weeks or placebo in addition to standard wound care. The authors reported significantly decreased ulcer surface area (−54.7 ± 28.8 percent versus +2.7 ± 47.2 percent; $p < 0.01$) and depth (−60.1 ± 13.8 percent versus −29.6 ± 12.6 percent; $p < 0.02$) after 16 weeks of therapy compared with the placebo group.[11]

Vitamin B_9 (Folic Acid)

Boykin et al. performed a retrospective cohort study (**Level of Evidence III**) with 29 patients receiving treatment for early-stage diabetic foot ulcer wounds. Wound surface areas were measured 4 weeks before supplementation, at the start of supplementation, and at 4-week follow-up. The authors reported a significant decrease in diabetic foot ulcer wound area after oral supplementation with 5 mg of vitamin B_9 (folic acid) daily for 4 weeks (−5.6 cm^2 versus −0.1 cm^2; $p < 0.05$) compared with the control group.[12]

Vitamin D

Razzaghi et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) with 60 patients receiving either 50,000 IU oral vitamin D supplementation or placebo every 2 weeks for 12 weeks for treatment of grade 3 diabetic foot ulcer wounds. The authors reported a significant reduction in ulcer length (−2.1 cm versus −1.1 cm; $p = 0.001$), width (−2.0 cm versus −1.1 cm; $p = 0.02$), depth (−1.0 cm versus −0.5 cm; $p < 0.001$), and erythema rate (100 percent versus 80 percent; $p = 0.01$) in patients receiving vitamin D supplementation compared with the placebo group.[13]

Vitamin E with Magnesium

Afzali et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) with 57 patients receiving either 400 IU vitamin E with 250 mg magnesium oral supplementation or placebo daily for 12 weeks for treatment of grade 3 diabetic foot ulcer wounds. The authors reported a significant reduction in ulcer length (−1.2 cm versus −0.8 cm; $p = 0.003$), width (−0.9 cm versus −0.7 cm; $p = 0.02$), and depth (−0.5 cm versus −0.2 cm; $p = 0.02$) in the supplementation group compared with the placebo group.[14] A summary of these results is provided in Table 6.

Table 6. Summary of Results for Diabetic Ulcer Wounds

Four studies (**Level of Evidence I to III**) provided appropriate data for analysis; 170 patients with diabetic ulcer wounds underwent nutritional intervention with vitamins A, B_9, D, and E, and magnesium. Our review demonstrated:

- Reduced total ulcer surface area with topical vitamin A, oral vitamin B_9, oral vitamin D, or oral vitamin E and magnesium supplementation

Venous Ulcer Wounds

Vitamin B_9 (Folic Acid)

De Franciscis et al. performed a prospective, open intervention, controlled trial (**Level of Evidence II**) with 87 patients receiving either 1.2 mg of folic acid oral supplementation daily for 12 months in addition to standard wound care or standard wound care alone for treatment of chronic venous ulcers. The authors reported a significant increase in the rate of total ulcer area reduction per week (−1.1 cm^2 versus −0.92 cm^2; $p < 0.05$) and the rate of definitive wound closure (78.8 percent versus 63.3 percent; $p < 0.05$) in patients receiving oral vitamin B_9 (folic acid) supplementation compared with the control group.[15]

Vitamin D

Burkiewicz et al. performed a prospective, double-blind, placebo-controlled trial (**Level of Evidence II**) with 52 patients receiving either 50,000 IU oral vitamin D supplementation or placebo weekly for 8 weeks for treatment of venous leg ulcers. The authors reported no significant wound improvement or ulcer size reduction compared with the placebo group ($p = 0.79$).[16]

Vitamin E

Lee performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) with 57 patients receiving treatment for chronic venous stasis ulcer wounds. The authors reported no significant improvement in the rate of wound healing between patients receiving oral tablets of vitamin E versus placebo ($p = 0.7$).[17]

Zinc

Strömberg and Agren performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence II**) with 37 geriatric patients undergoing treatment of venous leg ulcers with topical application of zinc oxide dressing. The authors reported improved wound healing (83 percent versus 42 percent; $p < 0.05$) and significant reduction in ulcer size (−3.2 cm^2 versus −1.5 cm^2; $p < 0.05$) at 8-week follow-up in the zinc-treated group compared with the placebo group.[18] Two years later, Eriksson performed a randomized, controlled trial (**Level of Evidence II**) with 34 patients receiving topical zinc dressing for treatment of venous leg ulcers and reported no significant improvement in ulcer size or volume when compared with the placebo group.[19]

Hallböök and Lanner[20] and Husain[21] independently performed randomized, single-blind,

placebo-controlled trials (**Level of Evidence I**) with a combined 154 patients receiving oral zinc supplementation for treatment of venous ulcers. The authors reported significantly shorter time to definitive wound closure in patients with serum zinc concentrations above 110 μg/dl or after receiving oral supplementation with 200 mg of zinc sulfate three times daily for 18 weeks ($p < 0.001$).[20,21] A summary of these results is provided in Table 7.

Digital Ulcer Wounds

Vitamin E

Fiori et al. performed a randomized, controlled trial (**Level of Evidence II**) to investigate the efficacy of vitamin E topical gel for treatment of digital ulcers in 27 patients with scleroderma. The authors reported a significant reduction in time to definitive wound closure (13.2 weeks versus 20.9 weeks; $p < 0.001$) in patients receiving topical vitamin E versus placebo.[22]

Skin Incision Wounds

Vitamin A

Tan and Tope performed a prospective, open-label, controlled trial (**Level of Evidence II**) with 29 patients undergoing Mohs surgery and reconstruction for skin cancer extirpation, both with and without the concomitant use of oral acitretin (vitamin A derivative) and found no significant differences in the rates of infection, dehiscence, or hypertrophic scarring compared with control group.[23]

Vitamin C with Zinc

Odgaard et al. performed a randomized, single-blind, placebo-controlled trial (**Level of Evidence I**) with 79 patients receiving oral vitamin C and zinc supplementation for treatment of surgical skin incisions. The authors reported significantly improved pain ($p = 0.21$), pruritus ($p = 0.026$), and overall assessment of the scar ($p = 0.033$) in the patient scale of the Patient and Observer Scar Assessment Scale but no significant differences in vascularity, pigmentation, thickness, relief, pliability, or surface area between groups.[24]

Vitamin C

Yun et al. performed a randomized controlled trial (**Level of Evidence I**) with 80 patients receiving either topical silicone gel containing vitamin C twice daily for 6 months, or no adjuvant topical therapy for postoperative facial surgical scar reduction. The authors reported a significant decrease in scar elevation ($p = 0.026$), erythema ($p = 0.025$), and melanin index ($p = 0.045$) in the supplementation group compared with the nontreated group at 6-month follow-up.[25]

Vitamin E

Zampieri et al. performed a randomized, single-blind, placebo-controlled trial (**Level of Evidence I**) with 428 pediatric patients to investigate the efficacy of topical vitamin E gel in keloid prevention. Patients receiving topical vitamin E gel experienced a significantly lower incidence of keloid formation (0 percent versus 6.5 percent; $p < 0.05$) and significantly higher satisfaction with cosmesis (96 percent versus 78 percent; $p < 0.05$) at 6-month follow-up compared with the petrolatum-only placebo group.[26] However, when Stanizzi et al. performed a randomized controlled trial (**Level of Evidence I**) with 60 patients undergoing treatment for skin graft donor sites, the authors reported no significant differences in outcomes or time to wound closure in patients receiving topical vitamin E compared with the placebo group.[27]

Vitamin K

Pazyar et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) with 63 patients receiving 1% topical vitamin K cream versus Eucerin (Beiersdorf AG, Hamburg, Germany) ointment twice daily for 2 weeks for treatment of skin incision wounds secondary to nevi, skin tag, or cherry angioma excisions. The authors reported no significant differences in outcomes or time to definitive wound closure (10.6 days versus 12.4 days; $p = 0.6$) in patients receiving topical vitamin K compared with the placebo group.[28]

Zinc

Pories et al. performed a randomized controlled trial (**Level of Evidence II**) with 20 patients to investigate the efficacy of oral zinc supplementation in the acceleration of wound healing. The authors reported 43 percent shorter time to definitive wound closure in patients receiving 220 mg of oral zinc three times per day

Table 7. Summary of Results for Venous Ulcer Wounds

Seven studies (**Level of Evidence I and II**) provided appropriate data for analysis; 421 patients with venous ulcer wounds underwent nutritional intervention with vitamins B_9, D, and E, and zinc. Our review demonstrated:

- Reduced total ulcer surface area and time to definitive wound closure with oral vitamin B_9 supplementation
- Reduced time to definitive wound closure with oral zinc supplementation
- No benefit on wound outcomes with oral vitamin D or oral vitamin E supplementation
- Heterogeneous data on time to definitive wound closure with topical zinc supplementation

compared with the nonsupplemented control group ($p < 0.01$).[29] However, Barcia performed a randomized controlled trial (**Level of Evidence II**) with 20 patients receiving 220 mg of oral zinc supplementation for treatment of surgical skin wounds and concluded that zinc supplementation was not a significant factor in accelerating granulation tissue production or reducing the overall time to wound closure.[30]

Zinc and Magnesium

Pastorfide et al. conducted a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) with 85 obstetric and gynecologic patients receiving either dual topical therapy with zinc chloride spray and magnesium hydroxide ointment or placebo spray and placebo ointment applied twice daily for 7 days for treatment of abdominal and perineal incisional wounds. The authors reported a significantly increased rate of definitive wound closure by postoperative day 4 (68.8 percent versus 37.8 percent; $p < 0.05$), reduced rate of infection (6.3 percent versus 18.9 percent; $p < 0.05$), and reduced rate of dehiscence (0 versus 8.1 percent; $p < 0.05$) in the supplementation group compared with the placebo group.[31] A summary of these results is provided in Table 8.

Hypertrophic Scars

Vitamin D

Van der Veer et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence II**) with 30 patients to evaluate the efficacy of topical vitamin D in preventing or reducing hypertrophic scar formation. Patients received either calcipotriol 50 μg/g ointment, or vehicle only (placebo group), twice daily for 3 months. The authors reported no significant difference in the incidence of hypertrophic scar formation between the vitamin D–treated scars and placebo.[32]

Vitamin E

Palmieri et al. performed a randomized, single-blind, placebo-controlled trial (**Level of Evidence I**) with 80 patients to evaluate the efficacy of vitamin E–infused silicone sheets in improving the appearance of hypertrophic scars. Patients receiving topical vitamin E were more likely to show significant improvement in scar appearance according to the Scott-Husskinson scale at 4-week (85 percent versus 55 percent; $p < 0.01$) and 8-week (95 percent versus 75 percent; $p < 0.05$) follow-up compared with the silicone-only placebo group.[33]

In addition, Perez et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence II**) with 30 patients to determine the efficacy of over-the-counter 0.5% hydrocortisone, silicone, and vitamin E lotion versus placebo in enhancing the cosmesis of hypertrophic scars. The authors reported significant improvement of scar appearance ($p < 0.01$) according to the observer scale of the Patient and Observer Scar Assessment Scale and subjective assessment ($p = 0.04$) and significant reduction in scar volume ($p = 0.01$), length ($p = 0.02$), induration ($p < 0.01$), erythema ($p < 0.01$), and pigmentation alteration ($p < 0.01$) compared with the placebo group.[34]

In contrast, Khoo et al. performed a randomized, double-blind, placebo-controlled trial (**Level of Evidence I**) in 122 patients receiving 5% topical vitamin E ointment for prevention of hypertrophic scar formation and reported no significant wound benefit. The authors concluded that 5% topical vitamin E ointment applied twice daily for 6 weeks did not significantly improve the appearance, vascularity, or incidence of hypertrophic scar formation at 4-month follow-up.[35] A summary of these results is provided in Table 9.

Table 8. Summary of Results for Skin Incision Wounds

Nine studies (**Level of Evidence I and II**) provided appropriate data for analysis; 864 patients with surgical skin incision wounds underwent nutritional intervention with vitamins A, C, E, and K; magnesium; and zinc. Our review demonstrated:

- Reduced scar elevation, erythema, and hyperpigmentation with topical vitamin C supplementation
- Improved patient-reported pain, pruritus, and satisfaction with scar cosmesis with oral vitamin C supplementation
- Reduced incidence of keloid formation with topical vitamin E supplementation but no effect on total time to definitive wound closure
- Reduced time to definitive wound closure, incidence of infection, and rate of wound dehiscence with topical magnesium and zinc supplementation
- No benefit on wound outcomes with topical vitamin A or topical vitamin K supplementation
- Heterogeneous data regarding time to definitive wound closure with topical zinc supplementation

Table 9. Summary of Results for Hypertrophic Scars

Four studies (**Level of Evidence I and II**) provided appropriate data for analysis; 262 patients with hypertrophic scar wounds underwent nutritional intervention with vitamins D and E. Our review demonstrated:

- No benefit on wound outcomes with topical vitamin D supplementation
- Heterogeneous data regarding incidence and improved cosmesis with topical vitamin E supplementation

Sinonasal Wounds

Vitamin A

Fang et al. performed a randomized, single-blind, within-subject, placebo-controlled trial (**Level of Evidence II**) with 30 patients to evaluate the efficacy of topical vitamin A ointment versus petrolatum-only placebo in promoting sinonasal wound healing and preventing or reducing adhesion formation. The authors reported significantly lower Lund-Kennedy scores for scar and adhesion formation (0.23 versus 0.53; $p < 0.05$) and significantly larger mean antrostomy size (0.70 cm^2 versus 0.57 cm^2; $p < 0.01$) at 12-month follow-up in the vitamin A–treated side versus placebo.[36]

DISCUSSION

Nutritional intervention has been shown to improve wound outcomes.[37,38] However, the role of micronutrient intervention in the treatment of specific wound types remains unclear. In this qualitative review of the literature, 36 studies explored the effect of micronutrient interventions on wound care outcomes. The majority of the studies included were Level II studies.

For burn wounds, all three included studies reported improved wound outcomes. For pressure ulcer wounds, four of the seven studies reported improved wound outcomes, particularly with oral vitamin C and oral zinc supplementation. Oral vitamin B_9, copper, and selenium interventions were explored by only a single study.

For diabetic ulcer wounds, all four included studies reported improved wound outcomes in patients receiving topical vitamin A, oral vitamin B_9, oral vitamin D, or oral vitamin E supplementation. However, in a recently published Cochrane review, Moore et al. concluded that the currently available evidence remains uncertain, and more research is needed to clarify the impact of nutritional interventions on the healing of diabetic foot ulcer wounds.[39]

For venous ulcer wounds, four of the seven included studies reported improved wound outcomes, particularly with oral zinc supplementation. Oral vitamin B_9 was reported to improve wound outcomes but was investigated by only a single study.

For skin incision wounds, the majority of included studies reported no significant benefit to nutritional supplementation. However, topical magnesium and topical zinc were investigated by only a single study, which reported significant improvement in wound outcomes. Topical vitamin A was also investigated by only a single study and found to significantly improve wound outcomes. Interestingly, one study reported that oral vitamin C and zinc supplementation resulted in improved patient-reported pain, pruritus, and satisfaction with scar cosmesis.

For hypertrophic scar wounds, two of the three included studies exploring topical vitamin E reported improved outcomes. Topical vitamin D was investigated by a single study and not found to improve outcomes.

Our study is limited by the heterogeneity of reporting in included studies, many of which presented small sample sizes, lacked consistency in outcome reporting, and lacked baseline nutritional status reporting. Furthermore, the limited number of included studies treating digital ulcer and sinonasal wounds makes it difficult to support or refute the use of nutritional intervention for treating these types of wounds.

CONCLUSIONS

Overall, more high-quality research is warranted to clarify the efficacy of nutritional intervention on wound healing outcomes. However, based on the current evidence provided by this review, the use of specific nutritional interventions may improve outcomes when treating particular types of wounds, as follows:

- Burn wounds benefit from oral vitamin A, vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin D, vitamin E, zinc, parenteral calcium, copper, magnesium, selenium, and zinc supplementation.
- Pressure ulcer wounds benefit from oral vitamin B_9, vitamin C, copper, selenium, and zinc supplementation.
- Diabetic ulcer wounds benefit from topical vitamin A, oral vitamin B_9, oral vitamin D, oral vitamin E, and oral magnesium supplementation.
- Venous ulcer wounds benefit from oral vitamin B_9 and oral zinc supplementation.
- Digital ulcer wounds benefit from topical vitamin E supplementation.
- Skin incision wounds benefit from topical vitamin A, topical magnesium, and topical zinc supplementation.
- Hypertrophic scar wounds may benefit from topical vitamin E supplementation.
- Sinonasal wounds benefit from topical vitamin A supplementation.

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