



Wound Healing and Nutritional Status in Pressure Injury: Arginine, Zinc and the Weakness of the Trial Base

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Abstract

Arginine and zinc appear in pressure injury guidance on the strength of a trial base that will not carry the weight placed on it. The most substantial randomised study gave 200 malnourished adults with stage II to IV injuries an enriched formula or an isocaloric, isonitrogenous control for eight weeks, and found a greater reduction in ulcer area, 60.9 per cent against 45.2 per cent, an adjusted difference of 18.7 per cent (95% CI 5.7 to 31.8, $P = 0.017$). That result is real and it is also the strongest in the field. Three complications follow. The formula contained arginine, zinc and antioxidants together and was compared as a whole, so no component can be credited with the effect. The endpoint that moved was ulcer area; no other secondary endpoint differed. And a review of 33 trials in 7,920 participants concluded that the benefits of nutritional intervention remain uncertain, with every promising composition rated low or very low certainty and at most two trials standing behind any single nutrient. The named ingredients on the label are not the units in which the evidence exists.

Keywords: Pressure injury; Arginine; Zinc; Wound healing; Evidence quality

Introduction

Nutritional status and pressure injury are connected in both directions. Poor intake and low body reserves are associated with the development of injury, and an open wound adds to protein and energy requirements [1,2]. From that uncontroversial starting point, practice has moved to specific supplementation, and arginine and zinc are named on products and in guidance [3,4].

Arginine is a substrate for collagen synthesis and a precursor of nitric oxide, and zinc is a cofactor for enzymes involved in protein synthesis and epithelial repair [5,6]. Both propositions are mechanistically reasonable, and neither is what a clinician is actually asking when deciding whether to supply an enriched formula [7].

This review separates the mechanism from the trial base. It asks what the randomised evidence establishes, at what level of

certainty, and about which intervention.

Objective

This review sets out to establish four things from the published literature. First, what the largest randomised trial in the field found and about which endpoint. Second, whether any individual nutrient can be credited with the observed effect. Third, how much evidence stands behind each named component. And fourth, what the certainty ratings imply for how the guidance should be read.

Literature Review

The strongest result: A multicentre, blinded, randomised trial enrolled 200 malnourished adults with stage II, III and IV pressure ulcers in long-term and home care, and gave 400 mL per day of an energy-dense, protein-rich oral formula enriched with arginine, zinc and antioxidants, or an equal volume of an isocaloric, isonitrogenous control, for eight weeks [8]. The primary endpoint was the percentage change in ulcer area. Reduction was 60.9 per cent (95% CI 54.3 to 67.5) with the enriched formula against 45.2 per cent (38.4 to 52.0) with the control, an adjusted mean difference of 18.7 per cent (5.7 to 31.8, $P = 0.017$) [8]. A reduction of 40 per cent or more was also more frequent, at an odds ratio of 1.98 (1.12 to 3.48, $P = 0.018$) [8].

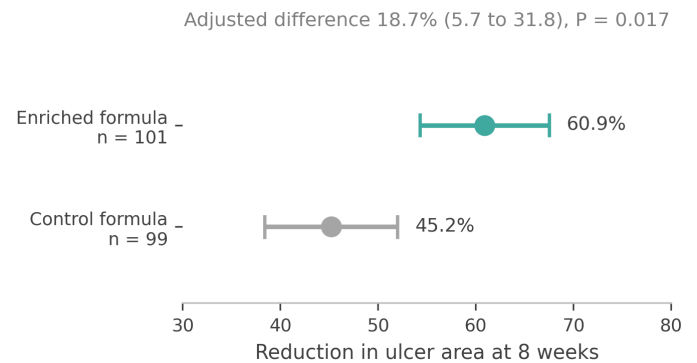


Figure 1: Reduction in ulcer area at eight weeks, by arm [8]

What the control condition establishes: The comparator matters more here than the intervention. Because the control was matched for calories and nitrogen, the difference cannot be attributed to energy or protein, which earlier trials in this field had failed to control [8]. That is the trial's principal methodological contribution and the reason it is cited. It narrows the candidate explanations to the enrichment, and stops there [8,9].

The attribution problem: The enrichment was arginine, zinc and antioxidants supplied together in a single formula and compared as a whole (Figure 2) [8]. A trial of a mixture answers a question about the mixture. Nothing in the design allows the effect to be assigned to arginine, or to zinc, or to the antioxidants, in any proportion [8,9]. Guidance and product labelling nevertheless name the components individually, which invites the inference that each carries evidence of its own [3,4,10].

Table 1: What the trial design permits to be concluded [8]

Which endpoint moved: Both positive results concern the same quantity measured two ways, the area of the wound at eight weeks and the proportion achieving a 40 per cent reduction in that area [8]. No difference was found in any other secondary endpoint reported [8]. Area reduction over a fixed window is a reasonable measure of progress, but it is not the same as healing, and a treatment that accelerates early contraction without changing the eventual outcome would produce this pattern [8,11].

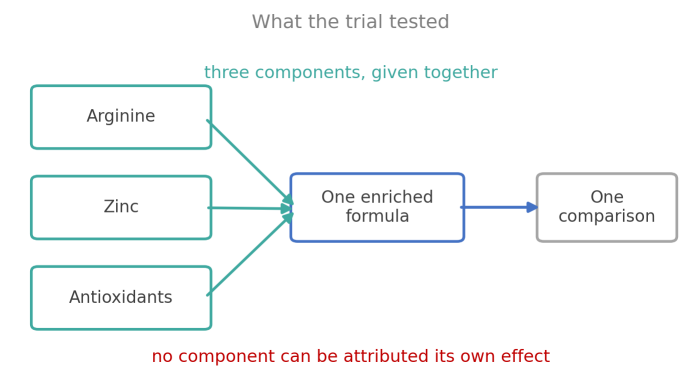


Figure 2: One formula, three components, one comparison [8]

Element	What was compared	What follows
Energy and protein	Matched in both arms	Excluded as explanation [8]
Arginine	Given with two others	Not separately tested [8]
Zinc	Given with two others	Not separately tested [8]
Antioxidants	Given with two others	Not separately tested [8]
The formula as a whole	Against isocaloric control	18.7% difference [8]

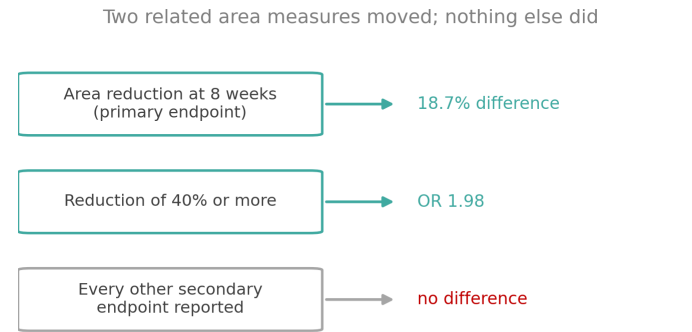


Figure 6: Endpoints that differed and endpoints that did not [8]

What the pooled evidence says: A systematic review published in 2024 included 33 randomised trials with 7,920 participants, searching to May 2022 [12]. Its conclusion was that the benefits of nutritional interventions for prevention and treatment are uncertain, and that there may be little or no difference compared with standard nutrition or placebo [12]. Several compositions, including protein with arginine, zinc and antioxidants, were described as promising approaches to increasing healing slightly, with the underlying evidence rated low or very low certainty [12].

Table 2: The named questions and the evidence available for each

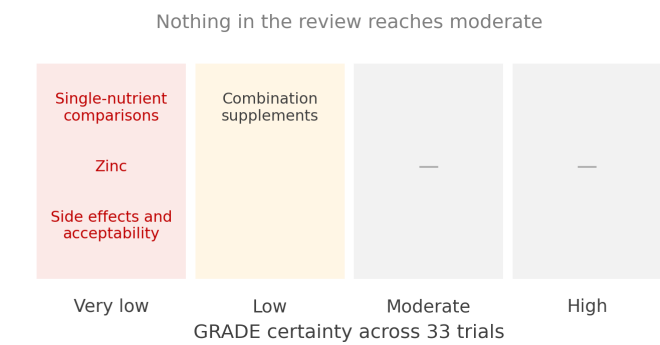


Figure 4: Certainty ratings across the reviewed evidence [12]

How thin the single-nutrient evidence is: The review found the evidence very uncertain about vitamin C, different doses of arginine, fatty acids with antioxidants, protein, a specialised amino acid mixture, ornithine alpha-ketoglutarate and zinc, with one or two studies contributing to each (Figure 3) [12]. Zinc, which appears by name in guidance and on labels, is supported at that level [12]. An earlier meta-analysis restricted to enriched formulas found a greater reduction in ulcer area of 15.7 per cent (95% CI 1.5 to 29.9 greater, $P = 0.030$) with substantial heterogeneity at 58.6 per cent, which is consistent in direction with the trial and wider in interval [9].

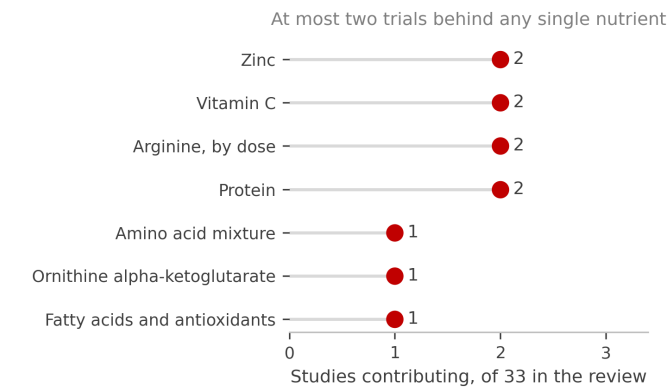


Figure 3: Studies contributing to each single-nutrient comparison [12]

Prevention is a separate and weaker question: The earlier version of the same review pooled eight trials with 6,062 participants comparing mixed nutritional supplements with standard hospital diet for preventing pressure ulcers, and found a risk ratio of 0.86 (95% CI 0.73 to 1.00) at $P = 0.05$ [13]. The interval touches unity and 4,015 of the 6,062 participants came from a single trial, so the pooled figure describes that trial more than it describes the field (Figure 5) [13]. The current review reports no clear evidence that nutritional intervention reduces the development of pressure ulcers [12].

Table 3: Four claims that are routinely stated as one

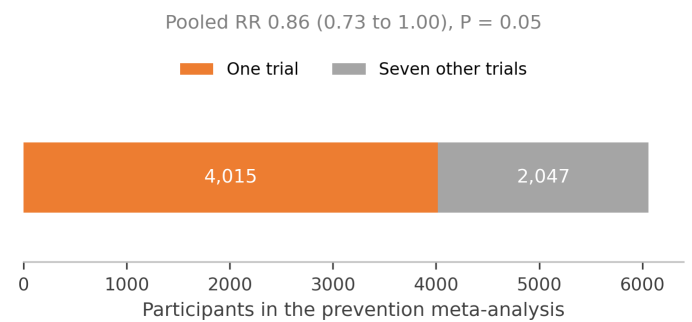


Figure 5: Where the prevention meta-analysis got its participants [13]

Question	What the evidence supports
Does the enriched formula help?	Area reduction, moderate trial [8]
Does arginine help by itself?	One or two studies, very low [12]
Does zinc help by itself?	One or two studies, very low [12]
Does supplementation prevent injury?	No clear evidence [12]
Do the supplements cause harm?	Uncertain, very low [12]

Who the trial population was: Participants were malnourished, able to drink oral supplements, and living in long-term care or receiving home care [8]. Each of those conditions narrows the applicable population, and the first is the most consequential, since a nutritional intervention tested in malnourished patients cannot be assumed to act the same way in adequately nourished ones [8,14]. Trials in non-malnourished patients exist but are smaller and were not designed to answer the same question [14,15].

Why the mechanism does not settle it: Arginine's role in collagen synthesis and nitric oxide production, and zinc's role as an enzyme cofactor, are established in biochemistry and do not depend on the clinical trials [5,6,16]. But a nutrient that is required for repair produces a clinical benefit from supplementation only where supply is limiting, and whether it is limiting in a given patient is exactly what the biochemistry does not say [16,17]. This is the same reason a deficiency state and a supplementation effect are separate findings [17,18].

Level of claim	Status
Nutrients are required for repair	Established biochemistry [5,6]
Deficiency impairs healing	Supported, observational [17,18]
Supplementing an enriched formula helps	One trial, area endpoint [8]
Supplementing a named nutrient helps	One or two studies each [12]

Assessment comes before supplementation: Both the review and clinical guidance place nutritional screening and assessment ahead of any particular product, and the review authors state that people who are malnourished or at risk should receive expert nutritional assessment and intervention [3,12]. That recommendation does not depend on the disputed trial evidencg,

because it addresses undernutrition rather than wound healing specifically [12,19]. Screening tools for this population have been compared and differ in what they capture, so prevalence of risk varies with the instrument [19,20,21].

What the guidance actually says: International guidance recommends considering a high-calorie, high-protein formula with arginine, zinc and antioxidants for adults with stage II or greater injury who are malnourished or at risk, and states the strength of that recommendation alongside the quality of its supporting evidence [3,4]. Read with the ratings attached it is consistent with the trial base. Read as a list of ingredients it is not, and the second reading is the one a product label encourages [3,10,22].

Cost and opportunity: Enriched formulas are more expensive than standard oral nutritional supplements, and analyses in this area have argued cost-effectiveness from reduced wound care intensity rather than from healing rates alone [9,23]. Where the healing benefit rests on an area endpoint at eight weeks, an economic case built on it inherits that limitation [8,23]. The comparison that matters practically is against adequate standard nutrition, not against nothing, and that is the comparison the isocaloric control provides [8,24].

What the wider wound literature adds: Reviews of nutrition in chronic wounds generally and in surgical healing describe the same structure, a strong physiological rationale with trial evidence that is small, heterogeneous and short [16,25,26]. Work on protein and energy requirements in wound healing supports ensuring adequacy rather than exceeding it, and the marginal benefit of supply beyond sufficiency is where the evidence is weakest across all of these fields [24,26,27]. Reporting standards for wound trials have been criticised on the same grounds, including inconsistent endpoint definition, which is part of why pooling is difficult [11,28,29].

Why the trials are small: Pressure injury trials recruit from a population that is old, comorbid and frequently unable to consent, in settings without research infrastructure, and follow-up is interrupted by death and transfer [12,30,31]. These are structural obstacles rather than oversights, which is why the recommendation for larger trials with similar nutrient compositions has been made repeatedly without being met [12,30]. Any realistic reading of this field has to treat the small trial base as a durable feature rather than a temporary gap [12,31,32].

Observational work in specific populations: Series in patients with spinal cord injury and pragmatic studies in mixed chronic wounds have reported outcomes with arginine-enriched supplements outside the randomised setting [33,34]. They describe what happens in patients who received and tolerated the product, which is useful for feasibility and unhelpful for effect size, since the comparison that would establish the latter is absent [33,34]. Read alongside the trial they neither strengthen

nor weaken it; they populate the gap between an eight-week area endpoint in malnourished long-term care residents and the range of patients to whom the product is offered [8,33,34].

What would settle the component question: A factorial design, in which arginine and zinc were varied independently against a common isocaloric base, would establish what the current trials cannot [8,12]. Nothing prevents such a trial in principle, and the recruitment obstacles that limit this field apply to it no more than to the studies already conducted [30,31]. Its absence is why guidance naming individual nutrients rests on a mixture trial, and why that gap has persisted through successive editions of the review without narrowing [12,13].

Method

This is a narrative review of published literature. Sources were assembled by searching the indexed literature for randomised trials, systematic reviews and clinical guidance concerning nutritional supplementation in adults with, or at risk of, pressure injury, with precedence given to randomised evidence with a controlled comparator and to reviews that publish certainty ratings [8,12].

Effect estimates are reproduced as their authors published them, with the interval and the certainty rating attached. Where a review recorded the number of studies behind a comparison, that number is carried with the estimate, since in this field it is the more informative quantity [12].

No new patient data were collected and no search protocol was registered, so this is not a systematic review. Supplement compositions are described as the formulations trials used, not as recommendations for any individual.

Concluding Remarks

The evidence supports a narrower claim than the one the labels make. An enriched formula produced a greater reduction in ulcer area than an isocaloric, isonitrogenous control in malnourished patients over eight weeks. That finding is well designed and it stands.

It does not establish that arginine works, or that zinc works, because neither was tested alone. At most two trials stand behind any single nutrient in the field, and the review that assembled all 33 concluded that the benefits remain uncertain. The named ingredients are units of marketing and of guideline prose; they are not units in which the trial evidence exists.

The practical implication is not to withhold enriched formulas from malnourished patients with open injuries, which the guidance supports and the trial evidence is consistent with. It is to stop reasoning about the components separately, and to recognise that identifying and correcting undernutrition rests on firmer ground than any claim about a specific nutrient.

Study Limitations

The trial base is small, heterogeneous in formulation and endpoint, and largely restricted to malnourished patients in long-term and home care, so extrapolation to acute settings and to adequately nourished patients is not supported. Area reduction over a fixed window predominates as an endpoint, and its relationship to complete healing is not established in these studies.

Certainty ratings in the reviewed evidence are low or very low throughout, which means the estimates constrain the truth weakly in both directions. An absence of demonstrated benefit for individual nutrients reflects the absence of trials that tested them, not evidence that they are inert.

The direction of the error matters: Treating the mixture result as evidence for each component overstates the case in one direction, but dismissing the mixture result because the components were not separated overstates it in the other [8,12]. The trial was well designed for the question it asked, and its isocaloric control makes it more informative than most of what surrounds it [8,9]. What does not follow is the ingredient-level reasoning that the label invites, and the distinction is worth holding precisely because the underlying finding is sound [8,10,22].

How this reads at the bedside: For a malnourished patient with an established injury, the guidance and the trial point the same way, and the decision is not finely balanced [3,8]. The uncertainty bites elsewhere: in adequately nourished patients, where the trial population does not reach; in prevention, where no clear effect has been shown; and in any decision that turns on one named nutrient rather than on the formula as supplied [8,12,14]. Those are three different questions and only the first has a trial behind it [8,12].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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