Micronutrients, Arginine, and Glutamine: Does Supplementation Provide an Efficient Tool for Prevention and Treatment of Different Kinds of Wounds?

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Significance: Wound-healing complications are a clinical problem with a considerable socioeconomic burden. Since several nutrients play a physiological role in wound healing, supplementation of these nutrients may improve wound healing.

Recent Advances: Oral nutritional supplements and enteral formulas providing arginine, glutamine, and micronutrients such as ascorbic acid and zinc should improve the healing of pressure ulcers (PU) and the healing of surgical, traumatic, and burned wounds. Is their efficacy proved from clinical intervention trials?

Critical Issues: Formulas that are rich in energy, protein, arginine, vitamin C, and zinc can improve PU healing, whereas their efficacy for PU prevention is less clear. High-dose supplementation of vitamin C, zinc, and pantothenic acid may improve the healing of surgical wounds in healthy subjects. Arginine lowers the risk of fistulas in patients undergoing elective surgery due to gastrointestinal cancer. However, formulations also enriched with *n*-3-fatty acids and ribonucleic acids lower the risk of several wound complications, thus being more effective than isolated arginine. Glutamine and antioxidant micronutrients (vitamin C and E, zinc, selenium, and copper) can improve the healing of surgical, traumatic, and burned wounds.

Future Directions: Considerable evidence suggests that formulations, indicated especially for critically ill patients, support the healing of PU and the healing of surgical and burned wounds. However, their optimal composition with regard to the dose of individual components has to be determined in future studies. Further well-designed trials should investigate the impact of certain nutrients for the prevention of PU and for the healing of surgical wounds in healthy subjects.

SCOPE AND SIGNIFICANCE

WOUND HEALING is a complex process that is orchestrated over time by an interaction of soluble mediators, blood cells, and parenchymal cells.¹ Wound healing requires energy, protein, a variety of vitamins and trace elements, and certain amino acids (arginine, glu-

tamine).^{2,3} This raises the question whether supplementation of selected nutrients, known to be indispensable for wound healing, is an efficient tool for the treatment of different kinds of wounds and for the prevention of pressure ulcers (PU) in patients with a high risk for PU.

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Abbreviations and Acronyms

BMI = body mass index
BSA = body surface area, burned
BW = body weight
EPA = eicosapentanoic acid
FA = fatty acid
GLA = gamma-linolenic acid
i.v. = intravenous application
n.d. = no data available
ONS = oral nutritional supplements
PU = pressure ulcers
PUSH = Pressure Ulcer Scale for Healing
RCT = randomized controlled trial

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**Abbreviations
and Acronyms (continued)**

RE = retinol equivalent

SD = standard deviation

SEM = standard error of the mean

TE = tocopherol equivalents

Vit = vitamin

TRANSLATIONAL RELEVANCE

From studies performed *in vitro* and with animals, it is well known that several nutrients are essential for wound healing. For example, retinol stimulates the proliferation and differentiation of epithelial cells and collagen synthesis.⁴ Ascorbic acid stabilizes collagen.⁵ Zinc is a cofactor of several enzymes and a transcription factor of several genes that are involved in proliferation.⁶ Arginine provides metabolites that are indispensable for collagen formation, cell proliferation, and angiogenesis.⁷ Glutamine provides energy and DNA bases in rapidly proliferating cells.⁸ Hence, an increased intake of these nutrients by supplements may improve wound healing, thus being of interest in wound care.

CLINICAL RELEVANCE

Wound-healing complications are the most expensive complications after surgery, considering annual costs of about US\$38 billion in the United States. The costs for the treatment of chronic wounds (venous ulcers, PU, and diabetic wounds) were estimated to amount to US\$25 billion. Since aging is associated with a higher risk for chronic wounds, the increasing life expectancy in industrialized countries will increase the socioeconomic burden.⁹ Since malnutrition impairs wound healing,² the use of efficient dietary supplements for wound healing is of great interest in wound care.

**DIETARY SUPPLEMENTS
TO SUPPORT WOUND HEALING**

Nowadays, several nutritional supplements, designed for patients with burns or chronic wounds to improve wound healing, are available for oral (oral nutritional supplements [ONS]) or enteral application. They provide large amounts of

ascorbic acid, zinc, arginine, and partly α -tocopherol, selenium, and copper. Supplements with arginine, omega-3-fatty acids, and nucleotides as key ingredients should stimulate the immune response and prevent an inappropriate inflammation. These formulas for immunonutrition are designed for critically ill patients, especially for those with surgical wounds or PU. Glutamine is offered either in an isolated form or as an ingredient of enteral formulations for critically ill patients suffering from trauma, burns, or surgery.¹⁰

**EFFICACY OF DIETARY
SUPPLEMENTS ON WOUND
HEALING—RESULTS
FROM HUMAN
INTERVENTION STUDIES**
Arterial and venous leg ulcers

The study of Husain, published in *The Lancet* in 1969, was the first randomized controlled trial (RCT) that investigated the effect of an oral zinc supplementation on leg ulcer healing.¹¹ Encouraged by his observation that supplementation of 150 mg/day zinc for 2–3 weeks accelerated the healing of leg ulcers,¹¹ zinc has become of great interest for wound care and several RCT were following. However, the meta-analysis of RCT of Wilkinson¹² did not find a beneficial effect of zinc supplementation on leg ulcer healing. However, the number of included studies was low ($n=4$), their quality was poor, and their sample size was too small to detect a significant effect for supplementation with zinc. Actually, there is no evidence to supplement zinc for the treatment of venous or arterial leg ulcers.¹²

Prevention and treatment of PU

The impact of ONS for the prevention of PU was investigated in elderly patients (mean age 81–83 years) with critical illness (e.g., stroke, heart failure, dyspnea, fracture, cancer,

infectious or digestive disease),¹³ or hip fracture,^{14–16} being at risk for PU due to immobilization (Table 1). The given ONS provided energy (254–400 kcal/day), protein (20–31 g/day), partly fat and carbohydrates, and several micronutrients such as vitamin C, E, and zinc. The intake of an ONS reduced the incidence of PU in the studies of Hommel *et al.*¹⁶ and Bourdel-Marchasson *et al.*¹³ if a multivariate analysis was performed while taking into account several risk factors. Houwing *et al.* did not observe any differences between verum and placebo groups, neither in PU incidence nor in further PU-related parameters.¹⁵ Since this study was underpowered,¹⁵ it does not allow any conclusions on the efficacy of the given ONS for the prevention from PU. In the study of Delmi *et al.*, the number of incident PU was too low for statistical evaluation.¹⁴ Theilla *et al.* found a lower PU incidence in patients who received an enteral formula enriched with protein (114 mg), ascorbic acid (914 mg), α -tocopherol (230 mg tocopherol equivalents; TE), β -carotene (5.4 mg), eicosapentaenoic acid, and γ -linolenic acid compared with patients of the control group who were fed a non-enriched formula with lower amounts of protein (59 mg), ascorbic acid (300 mg), and α -tocopherol (54 mg TE).¹⁷ Hence, supplements enriched with energy, protein, and several micronutrients (vitamins A, C, E, and zinc) may contribute to the prevention from PU in patients at risk for PU.

Considering PU treatment (Table 2), Taylor *et al.* were the first who investigated the impact of nutritional supplements for PU treatment in surgical patients.¹⁸ In a double-blind, placebo-controlled trial, supplementation of 1,000 mg/day ascorbic acid reduced PU area in 84% of the patients (control group: 43%) and increased the healing rate by about 70% compared with the control.¹⁸ In a similar trial, also double blind and placebo controlled, but with multicenter design, supplementation of 1,000 mg ascorbic acid daily to institutionalized or hospitalized patients with PU for 12 weeks did not improve wound healing compared with the control group that received only 20 mg/day ascorbic acid.¹⁹ Further intervention studies with a controlled^{20–22} and uncontrolled^{23–26} design, providing an ONS enriched with protein, a couple of micronutrients, and partly with arginine, observed a reduction in PU area,^{21–23,25} Pressure Ulcer Scale for Healing (PUSH) score,^{20–22} and in the time for wound closure,²⁶ and a higher percentage of patients with complete wound closure.²⁴ Leigh *et al.*²⁷ did not find a treatment effect with regard to PUSH score, but they investigated the efficacy of one versus two servings of Arginaid® and

did not include an ONS-free control group. It is important to mention that RCT with beneficial effects on wound healing by ONS provided not only relatively high amounts of vitamin C (475–569 mg), but also high doses of zinc (17–30 mg), arginine (5.7–9 g), and protein (21–45 g).^{20–22} Data from studies with enteral formulas are scarce, as only a single study has been published so far.²⁸ Nevertheless, the results of this study²⁸ are in accordance to those studies providing ONS, also suggesting the beneficial effects on PU healing by a formula which is rich in protein as well as in micronutrients that are required for wound healing (Table 2).

Treatment of surgical wounds

The effect of supplementation of micronutrients, arginine, and glutamine in patients with surgical or traumatic wounds has been investigated in several clinical trials (Table 3).

More than 45 years ago, Pories *et al.*²⁹ have shown that supplementation of 150 mg/day zinc to healthy young men undergoing surgery accelerated wound healing compared with patients without zinc supplementation. Later studies performed by Vaxman *et al.* with healthy young patients undergoing surgery for tattoo removal provided ascorbic acid and pantothenic acid.^{30,31} Supplementation of 1,000 mg ascorbic acid plus 200 mg pantothenic acid increased the number of fibroblasts, the hydroxyproline content in skin/scars, and their mechanical resistance compared with the placebo group.³¹ In a similar study of the same group, supplementation of 3,000 mg ascorbic acid along with 300 mg pantothenic acid was not superior to the supplementation of 1,000 mg ascorbic acid plus 200 mg pantothenic acid with regard to most investigated parameters. Only the breaking strength of scars was higher in patients who received the larger dose of vitamin C and pantothenic acid.³⁰

Enteral supply of arginine (26 g/day for 5 days) to patients undergoing autografting as a part of reconstructive surgery increased the plasma concentration of arginine and citrulline, a metabolite generated in equimolar amounts such as nitric oxide by nitric oxide synthase. However, parameters of wound healing (neutrophil index, angiogenesis, and re-epithelialization) were not different from the placebo group that received isocaloric amounts of alanine.³² If arginine (30 g/day) was given intravenously in addition to the hospital diet, differences in wound healing (neutrophil index, angiogenesis, and percentage of re-epithelialization) between verum and control (arginine) did not occur either.³³ In several RCT of de Luis *et al.*,³⁴ arginine-enriched enteral

Table 1. Effect of supplements on the prevention of pressure ulcers

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Pressure ulcer risk and incidence	Results
Delmi <i>et al.</i> ¹⁴	59	Patients with femoral neck fractures Age: 82 ± 0.3 BMI: n.d.	Verum ONS Energy: 254 kcal Protein: 20.4 g Fat: 5.8 g Carbohydrates: 29.5 g Vit A: 750 IU Vit D: 25 IU Vit B, C, E: n.d. Control No supplementation	32 days (mean)	Randomized, controlled	Incidence of PU At orthopedic unit At recovery At 6 months	n=2 (V), n=3 (C) n=0 (V), n=3 (C) n=0 (V), n=2 (C) (no statistical evaluation)
Bourdel-Marchasson <i>et al.</i> ¹³	672	Critically ill patients, unable to move themselves and to eat independently, several comorbidities ^a Age: 83 ± 0.3 BMI: n.d.	Verum Three different ONS (Nutricia, Jacquemaire-Santé, Clintec-Sopharga) Energy: 400 kcal Protein: 30 g Fat: 8.6 g Carbohydrates: 48.8 g Vit C: 30 mg Zinc: 3.6 mg Control No supplementation	Up to 15 days or until discharge if patients stayed fewer than 15 days	Randomized (wards), controlled, multicenter study (19 wards)	Incidence of PU Risk for PU Norton score Kuntzmann score	V < C V < C V < C
Houwing <i>et al.</i> ¹⁵	103	Hip-fracture patients, not at terminal care, without metastatic hip fracture, insulin-dependent diabetes, renal or hepatic disease, and morbid obesity Age: 81 ± 1 BMI: 24.0 ± 0.4	Verum ONS (Cubitan®; Nutricia) Intake ^b Energy: 385 kcal Protein: 31 g Arginine: 4.6 g Vit C: 385 mg Vit E: 154 mg TE Zinc: 15 mg Carotenoids: 4 mg Placebo Caloric-free, water-based placebo	28 days or until discharge 10 days (median)	Double-blind, randomized, placebo-controlled, multicenter study (three centers)	Incidence of PU PU stage Stage I Stage II First day PU Days PU (sum) Total maximum wound size	V = P V = P V = P V = P V = P V = P
Hommel <i>et al.</i> ¹⁶	420	Patients with hip-fractures at risk for PU, ≥ comorbidities in V (36%) and in C (20%) Age: 81 ± 1 BMI: 24.3 ± 0.2	Verum ONS Energy: 300 kcal Vit A, B, C, E, β-carotene, zinc, selenium: n.d. Control No supplementation	Until discharge 11 days (mean)	Not randomized, controlled	Incidence of PU at discharge PU stage Stage I Stage II Stage III	V < C 46% V vs. 48% C 39% V vs. 66% C 14% V vs. 4% C (no statistical evaluation)

(continued)

Table 1. (Continued)

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Pressure ulcer risk and incidence	Results
Theilla <i>et al.</i> ¹⁷	95	Patients with acute lung injury, but without head trauma, cerebral bleeding, and coagulation disorders Age: 59 ± 2 BMI: 27.7 ± 0.6	Verum Enteral formula (Pulmocare, Ross Laboratories, Abbott) enriched with lipids (EPA, GLA), Vit A, C, E (Opexa, Ross Laboratories) Intake ^b Energy: 1,624 kcal Protein: 114 g Vit C: 914 mg Vit E: 230 mg TE β-carotene: 5.4 mg Control Enteral formula (Pulmocare, Ross Laboratories, Abbott) Intake ^b Energy: 1,420 kcal Protein: 59 g Vit C: 300 mg Vit E: 54 mg TE β-carotene: 0 mg	14 days	Randomized, controlled	Incidence of PU PU healing	V < C (d4, d7) V = C

Data on age (years) and BMI (kg/m²) are means ± SEM if not indicated otherwise. Means were calculated as weighted means from the data of individual groups if not provided by the authors. Missing SEMs were calculated by SDs or SEMs of individual groups.

^aComorbidities: stroke, heart failure, dyspnea, infectious diseases, digestive diseases, delirium, dehydration, lower limb fractures, cancer, neurological diseases, painful arthritis, deep venous thrombosis, miscellaneous medical diseases.

^bBased on mean intake of 77% of target dose.

BMI, body mass index; C, control group; EPA, eicosapentanoic acid; GLA, gamma-linolenic acid; n.d., no data available; ONS, oral nutritional supplement; P, placebo group; PU, pressure ulcers; TE, tocopherol equivalents; V, verum group; Vit, vitamin; SD, standard deviation; SEM, standard error of the mean.

Table 2. Effect of supplements on therapy of pressure ulcers

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of pressure ulcer healing	Results
Taylor <i>et al.</i> ¹⁸	20	Surgical patients with PU ^a Age: 75 (mean), 54–88 (range) BMI: n.d.	Verum Vit C, 1,000 mg (Merck) Placebo n.d.	30	Double blind, placebo controlled	PU area reduction Healing rate	V > P V > P
ter Riet <i>et al.</i> ¹⁹	88	Patients with PU (82% stage II/III), 23% with diabetes Age: n.d. BMI: V: 21.5, P: 20.7 (medians)	Verum Vit C, 1,000 mg (Roche) Placebo Vit C, 20 mg (Semperit)	84	Block-randomized, double-blind, placebo-controlled, multicenter study (11 nursing homes, 1 hospital)	Healing rate Healing velocity Healing volume reduction	V = P V = P V = P
Frias Soriano <i>et al.</i> ²³	39	Patients with PU, stage III/IV, partly with dementia, paralysis, fracture, diabetes, infection, and pneumonia Age: 75 ± 13 BMI: 22.9 ± 5.9	Verum ONS (Cubitan [®] ; Nutricia) Intake ^b Energy: 475 kcal Protein: 38 g Vit C: 474 mg Vit E: 71 mg Zinc: 17 mg	21	Not randomized, not controlled, multicenter study (10 hospitals)	PU area Healing rate Wound ground Granulation tissue Sphacelus Necrotic tissue Wound infection Wound malodour Infected ulcers Exsudation Wound pain PUSH score	V ↓ (week 0 vs. week 3) V ∅ (week 0 vs. week 1, 2, 3) V ↑ (week 0 vs. week 1) V ↓ (week 0 vs. week 3) V ↓ (week 0 vs. week 2, 3) V ↓ (week 0 vs. week 1, 2) V ↓ (week 0 vs. week 1, 2, 3) V ↓ (week 0 vs. week 2) V ↓ (week 0 vs. week 3) V ∅ (week 0 vs. week 1, 2, 3) V ↑ ∅, V2 ↓, C ↓, ΔC < ΔV1, ΔV2 (week 3)
Desneves <i>et al.</i> ²⁰	16	Inpatients with PU, stage II–IV, from aged care or spinal injury wards, without osteomyelitis, diabetes, and parenteral nutrition support Age: 73 ± 3, 37–92 (range) BMI: 23.6 ± 1.2, 16.4–28.1 (range)	Verum 1 ONS (Resource [®] ; Novartis) Energy: 500 kcal Protein: 18 g Vit C: 72 mg Zinc: 7.5 mg Verum 2 ONS (Resource [®] Arginaid [™] Extra; Novartis) Energy: 500 kcal Protein: 21 g Arginine: 9 g Vit C: 500 mg Zinc: 30 mg Control No ONS	21	Randomized, double blind, placebo controlled	PUSH score	V1 ∅ V2 ↓ (week 0 vs. week 2, 3) C ↓ (week 0 vs. week 3)

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Table 2. (Continued)

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of pressure ulcer healing	Results
Raffoul <i>et al.</i> ²⁴	9	Patients with deep limb ulcers or PU, unresponsive for conservative treatment, without wound infections and renal failure Age: 71 ± 3 BMI: 23.3 ± 1.0	Verum ONS (Clinutren [®] ; Nestle), 1–4 servings/day, one multivitamin tablet (Supradyn [®] ; Roche), 500 mg Vit C (Redoxon [®] ; Roche) Intake ^c Energy: 720 kcal Protein: 27 g Vit A: 4.04 mg RE Vit C: 752 mg Vit E: 19.6 mg Zinc: 10.2 mg Iron: 11.5 mg Selenium: 36 µg	15 (5 days before until 10 days after surgery)	Not controlled	Wound healing by d10 Days needed to complete healing Hydroxyproline on d10 in subcutaneous tissue	90% (median) 20 days (median) 11 mmol/cm (median)
Heyman <i>et al.</i> ²⁵	245	Patients with PU, stage II–IV, 40% diabetes, 35% cerebrovascular accident, 51% dementia, 44% multiple diagnoses, 78% wheelchair, and/or chair-bound Age: 82 ± 1 BMI: n.d.	Verum ONS (Cubitan [®] ; Nutricia), three servings/day Energy: 575 kcal Protein: 46 g Arginine 6.9 g Vit C: 575 mg Vit E: 87 mg Zinc: 21 mg	63	Not randomized, not controlled, multicenter study (61 long-term care facilities)	PU area Patients with complete wound closure Exsudate	V ↓ (week 3, 9 vs. week 0) 7% (week 16) 20% (week 49) V ↓
Cereda <i>et al.</i> ²¹	28	Patients with PU, stage II–IV, without chronic disease (e.g., diabetes mellitus, peripheral vascular disease, autoimmune, and neoplastic disorders) Age: 82 ± 2 BMI: 22.0 ± 1.8	Verum ONS (Cubitan [®] ; Nutricia), two servings/day, or enteral formula (Cubison [®] ; Nutricia), 1,000 mL/day Intake ^d by Cubitan [®] vs. Cubison [®] Energy (kcal): 475 vs. 950 Protein (g): 32 vs. 52 Arginine (g): 5.7 vs. 8.1 Vit C (mg): 475 vs. 361 Zinc (mg): 17 vs. 19 Control No supplement	84	Randomized, controlled, multicenter study (four long-term care facilities)	PU area Reduction in PU area PUSH score	V = C (week 2, 4, 6, 8, 12) V = C (week 2, 4, 6); V > C (week 8) V = C (week 2, 4, 6, 8); V < C (week 12) Regression model: Inverse association between PUSH score and arginine intake and the use of a disease-specific formula

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Table 2. (Continued)

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of pressure ulcer healing	Results
van Anholt <i>et al.</i> ²²	43	Patients with PU, stage III–IV, life expectancy ≥ 6 months, without undernutrition and palliative care Age: 75 ± 2 BMI: 24.7 ± 0.7	Verum ONS (Cubitan [®] ; Nutricia), three servings/day Intake ^d Energy: 569 kcal Protein: 45 g Arginine: 6.8 g Vit A: 541 mg RE Vit C: 569 mg Vit E: 86 mg TE Folic acid: 455 μ g Carotenoids: 4.5 mg Zinc: 20 mg Selenium: 145 μ g Copper: 3.0 mg Placebo n.d.	56	Multicenter, multicountry, randomized, controlled, double blind	PU area PUSH score Tissue type Ulcer closed or epithelialized (%) Ulcer Granulated or necrotic (%)	V < P (week 3, 5) V < P (week 4) V > P (week 4) V < P (week 4)
Brewer <i>et al.</i> ²⁶	35	Spinal-cord-injured patients with PU, stage II–IV, partly with diabetes, but without sepsis, chronic renal failure, metabolic disease, and diabetic food ulcers Age: 51 ± 2 BMI: n.d.	Verum ONS (Arginaid [®] , Nestlé Nutrition), two servings/day Energy: 33 kcal Carbohydrates: 8 g Arginine: 9 g Vit C: 310 mg Vit E: 120 mg TE Control (historical group) No ONS	Time until wound closure	Not randomized, controlled	Time for wound closure Healing rate	V < C V > C

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Table 2. (Continued)

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of pressure ulcer healing	Results
Ohura <i>et al.</i> ²⁸	50	Patients with PU, stage III–IV, 48% cerebral infarctions, 35% dementia, but without liver or renal disorders, severe diabetes mellitus, malignant tumor, unmanageable severe general condition, and unevaluable pressure ulcer wounds Age: 81 ± 1 BMI: 17.7 ± 0.5	Enteral formula (Racol [®] ; EN Otsuka Pharmaceutical) Verum vs. Control Energy (kcal): 1,384 vs. 1,092 Protein (g): 61 vs. 48 Fat (g): 31 vs. 24 Carbohydrates (g): 216 vs. 171 Vit A (mg RE): 1.6 vs. 1.2 Vit C (mg): 289 vs. 307 Vit E (mg TE): 9 vs. 7 Zinc (mg): 9 vs. 7 Copper (mg): 1.7 vs. 1.4 ONS (Arginaid [®] ; Nestlé Medical Nutrition), V1: one serving/day, V2: two servings/day Intake Verum 1 vs. Verum 2 ^d Energy (kcal): 15 vs. 30 Carbohydrates (g): 4 vs. 7 Arginine (g): 4.1 vs. 8.3 Vit C (mg): 143 vs. 285 Vit E (mg TE): 37 vs. 75	84	Randomized, controlled	PU area	V = C (week 0, 2, 4, 6); V < C (week 8, 10, 12)
Leigh <i>et al.</i> ²⁷	23	Inpatients with PU, stage II–IV, without sepsis, acute gastrointestinal surgery, and dialysis Age: 69 ± 4 (range: 31–92) BMI: 26.8 ± 1.6	ONS (Arginaid [®] ; Nestlé Medical Nutrition), V1: one serving/day, V2: two servings/day Intake Verum 1 vs. Verum 2 ^d Energy (kcal): 15 vs. 30 Carbohydrates (g): 4 vs. 7 Arginine (g): 4.1 vs. 8.3 Vit C (mg): 143 vs. 285 Vit E (mg TE): 37 vs. 75	21	Randomized	PUSH score	Effects by time, not by treatment, No impact from initial nutritional status assessed by SGA

Data on age (years) and on BMI (kg/m²) are means ± SEM. Means were calculated as weighted means from the data of individual groups if not provided by the authors. Missing SEMs were calculated by SDs or SEMs of individual groups.

^aDiagnoses: fractured neck of femur, rheumatoid arthritis, cerebrovascular accident, fractured pelvis, peripheral vascular disease, paraplegia, gastric ulcer, benign prostatic hypertrophy, diverticular disease, aortic aneurysm.
^bMean ingestion of 1.9 servings/day.

^cConsidering mean intake from target dose.

^dBased on a mean intake of 75% of target dose; PUSH, Pressure Ulcer Scale for Healing; RE, retinol equivalent; SGA, subjective global assessment; ↓, significant decrease; ∅, no significant changes; Δ, changes; ↑, significant increase.

Table 3. Effect of supplements on prevention and therapy of surgical/traumatic wounds

References	Number of subjects (n)	Patient population characteristics	Intervention: additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of wound healing	Results
Pories <i>et al.</i> ²⁹	20	Healthy men with surgical wounds Age: 25 (mean) BMI: n.d.	Verum Zinc, 150 mg Control No supplement	n.d.	Randomized, controlled	Time to wound closure Healing rate Wound volume (end of study)	V < C V > C V < C
Vaxman <i>et al.</i> ³⁰	40	Healthy subjects with ambulatory surgery for tattoo resection (7 and 14 days after starting supplementation) Age: V: 27 ± 1, P: 24 ± 1 BMI: n.d.	Verum Vit C, 1,000 mg, Pantothenic acid, 200 mg (Hoffmann-La Roche) Placebo n.d.	21	Randomized, double-blind, placebo-controlled	Skin/scars Fibroblast count (d8, d21) Hydroxyproline (d8, d21) Scars Width, complication score, pain, stress, and stiffness (d80) Hypertrophy, rigidity, and color (d80)	V > P V = P V = P V > P
Vaxman <i>et al.</i> ³¹	27	Healthy subjects with ambulatory surgery for tattoo resection (7 and 14 days after starting supplementation) Age: n.d. BMI: n.d.	Verum 1 Vit C, 1,000 mg, Pantothenic acid, 200 mg (Hoffmann-La Roche) Verum 2 Vit C, 3,000 mg, PA, 300 mg (Hoffmann-La Roche)	21	n.d.	Skin/scars Fibroblast count (d8, d21) Hydroxyproline (d8, d21) Scars Breaking strength (d80) Width, complications, pain, stress, elastic stiffness, rigidity, and pain (d80)	V1 ↑, V2 ↑, V1 = V2 V1 ↓, V2 ↓, V1 = V2 V2 > V1 V1 = V2
de Luis <i>et al.</i> ³⁴	47	Patients with oral and laryngeal cancer undergoing elective surgery ^a Age: 61 ± 2 BMI: 25.1 ± 0.7	Verum Enteral formula enriched with arginine (10.9 g ^b) and fiber Control Isocaloric, isonitrogenous enteral formula without arginine and fiber	≥ 10 ^c	Randomized, controlled	Wound-healing complications Fistulas Wound infection	V < C V = C
Oguz <i>et al.</i> ⁴⁰	109	Patients with colorectal cancer undergoing surgery, without metabolic disorders, emergency surgery, and abdominoperineal resection Age: 54 ± 10 BMI: 23.0 ± 2.5	Verum Glutamine (Dipeptiven®; Fresenius-Kabi), 1.0 g/kg BW, i.v. Control No glutamine	6 days pre- and 5 days postoperatively	Randomized, controlled	Wound-healing complications Wound infection Wound dehiscence Intra-abdominal abscess	V < C V < C V < C

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Table 3. (Continued)

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of wound healing	Results
de Luis <i>et al.</i> ³⁵	72	Patients with oral and laryngeal cancer undergoing elective surgery ^a Age: 62 ± 1 BMI: 24.5 ± 0.6	Verum Enteral formula enriched with arginine (17 g) Control Isocaloric, isonitrogenous enteral formula without arginine	≥ 10 ^f 16 ± 9 (mean ± SD)	Randomized, controlled	Wound-healing complications Fistulas Wound infection	V < C V = C
De Luis <i>et al.</i> ³⁶	72	Patients with oral and laryngeal cancer undergoing elective surgery ^a Age: 62 ± 1 BMI: 26.4 ± 0.7	Verum Enteral formula enriched with arginine (6.1 g) and fiber Control Isocaloric, isonitrogenous enteral formula without arginine	≥ 10 ^d	Randomized, controlled	Wound-healing complications Fistulas Wound infection	V < C V = C
Debats <i>et al.</i> ³²	18	Patients undergoing autografting as a part of reconstructive surgery ^e Age: 48 ± 3 BMI: 27.0 (mean)	Verum Arginine, 26 g, enteral (Bufa, Uitgeest) Placebo Alanine, 51.2 g (Bufa, Uitgeest), isocaloric amounts	5	Randomized, double blind, placebo controlled	Wound healing Neutrophil influx Angiogenesis Re-epithelialization Wound fluid Arginine Arginase-1, sum of nitrite + nitrate	V = P (d2, d5, d10) V = P (d2, d5, d10) V = P (d5, d10) V > P (d2, d5) V = P (d2, d5)
De Luis <i>et al.</i> ³⁷	115	Patients with oral and laryngeal cancer undergoing elective surgery ^a Age: 63 ± 1 BMI: 25.7 ± 0.4	Verum 1 Enteral formula highly enriched with arginine (20 g) Verum 2 Enteral formula enriched with arginine (12.3 g)	≥ 10 ^d	Randomized, double blind	Wound-healing complications Fistulas Wound infection	V < C V = C
Debats <i>et al.</i> ³³	35	Patients undergoing autografting as a part of reconstructive surgery ^e Age: 44 ± 3 BMI: 26.2 ± 1.0	Verum Arginine, 30 g, i.v. Placebo Alanine, 25.2 g, i.v. (isovolumetric, isonitrogenous amounts) (both: Bufa, Uitgeest)	5	Randomized, double blind, placebo controlled	Wound healing Neutrophil influx Angiogenesis Reepithelialization	V = P (d2, d5, d10) V = P (d0, d2, d5, d10) V = P (d5, d10)

(continued)

Table 3. (Continued)

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of wound healing	Results
Blass <i>et al.</i> ⁴¹	20	Trauma patients with disorders in wound healing ^f Age: V: 45, P: 46 (medians) BMI: V: 27.6, P: 25.8 (medians)	Verum ONS Glutamine plus® (Fresenius-Kabi), two servings/day Intake ^g Energy: 81 kcal Glutamine: 19 g Vit C: 480 mg Vit E: 160 mg TE β -carotene: 3.1 mg Zinc: 6.3 mg Selenium: 96 μ g Placebo Maltodextrine (Dr. Steidle) (isocaloric amounts)	14	Randomized, double blind, placebo controlled	Microcirculation in wound area (2 mm tissue depth) Oxygen saturation Relative haemoglobin Blood flow Blood velocity Vascular growth factor A (serum) Wound temperature Time to wound closure	V $\emptyset$, P $\downarrow$ V $\emptyset$, P $\emptyset$ V $\emptyset$, P $\emptyset$ V $\emptyset$, P $\emptyset$ V $\emptyset$, P $\emptyset$ V $\emptyset$, P $\emptyset$ V $\emptyset$, P $\emptyset$ V $\emptyset$, P $\emptyset$ V < P

Data on age (years) and on BMI (kg/m^2) are means $\pm$ SEM. Means were calculated as weighted means from the data of individual groups if not provided by the authors. Missing SEMs were calculated by SDs or SEMs of individual groups.

^aWithout severe impaired hepatic and renal function, ongoing infections, autoimmune disorders, ONS in previous 6 months, severe malnutrition (weight loss > 10%).

^bBased on own calculations considering an energy intake of 32 kcal/kg body weight/d and a mean body weight of 68 kg.

^cFormulation was given until patients could ingest at least 1,500 kcal and 1.0 g protein/kg BW/day orally.

^dFormulation was given until patients could ingest at least 1,700 kcal and 1.0 g protein/kg BW/day orally.

^eDue to burns, trauma, malignancy, and other reasons; exclusion criteria: kidney or liver failure, immune deficiency diseases, diabetes.

^fMain diagnosis: fractures, partly with soft tissue trauma; comorbidities: vascular diseases, diabetes mellitus, hypertension, dementia, pressure ulcer.

^gConsidering an intake of 96% of target dose.

BW, body weight; FA, fatty acid; i.v., intravenous application; $\uparrow$, significant increase; $\downarrow$, significant decrease; $\emptyset$, no significant changes.

Table 4. Effect of supplements on wound healing after burns

References	Number of subjects (n)	Patient population characteristics	Intervention; additional intake of nutrient/day	Period of supplementation (days)	Study design	Parameters of wound healing	Results
Zhou <i>et al.</i> ⁴²	40	BSA 50–80%, 20–40% with third degree burns Age: 42 ± 1 BMI: 21.4 ± 0.3	Verum Enteral nutrition (Ensure, Abbott), enriched with glutamine (Ajinomoto), 0.35 g/kg BW Placebo Enteral nutrition (Ensure, Abbott) without glutamine	12	Randomized, double blind, controlled	Participants with healed wounds (d30) Wound infections (d30)	V > P V < P
Peng <i>et al.</i> ⁴³	48	BSA 30–75% Age: 38 ± 11 BMI: n.d.	Verum Glutamine, 0.5 g/kg BW (Chongqing Yao You pharmaceutical), oral or enteral application Placebo Glycine, 0.5 g/kg BW	14	Randomized, double blind, placebo controlled	Healing rate	V > P
Berger <i>et al.</i> ⁴⁵	21	BSA > 20% ^a Age: 42 ± 3 BMI: n.d.	Verum 0.9% saline solution, i.v., enriched with Zinc: 21.5 ± 5.6 mg Selenium: 90 ± 24 µg Copper: 2.7 ± 0.7 mg Placebo 0.9% saline solution not enriched with zinc, selenium, and copper	14–21	Randomized, placebo controlled	Ratio of surface grafted to total body surface requiring surgery	V < P
Barbosa <i>et al.</i> ⁴⁶	32	Children > 10% BSA, with segments of second-degree injury ^b Age: 5 ± 1 BMI: n.d.	Verum Redoxon® (Roche Laboratories) Intake ^c Vit C: 900 mg Vit E: 400 mg TE Zinc: 7 mg Placebo n.d.	7	Randomized, double blind, placebo controlled	Time to wound healing	V < P
Pattanshetti <i>et al.</i> ⁴⁴	30	BSA 20–60% ^d Age: 31 ± 2 BMI: n.d.	Verum Isonitrogenous mixture enriched with glutamine (Glutammune®, Claris Lifesciences), 0.5 g/kg BW Control Isonitrogenous mixture without glutamine	Until complete wound healing or split thickness of grafting	Randomized, controlled	Time for wound healing	V < C

Data on age (years) and on BMI (kg/m²) are means ± SEM if not indicated otherwise. Means were calculated as weighted means from the data of individual groups if not provided by the authors. Missing SEMs were calculated by SDs or SEMs of individual groups.

^aExclusion criteria: foreseen imminent death, chronic cardiac failure, chronic liver disease, severe renal failure, and obesity.

^bExclusion criteria: > 50% BSA, polytrauma, brain trauma, tracheal intubation, mechanical ventilation, refractory shock, intolerance to oral/enteral nutrition, diabetes mellitus, cancer, chemo-/radiotherapy, organ failure, and chronic infection.

^cAverage values, recommendation, and intake were age dependent.

^dExclusion criteria: pre-existing severe cardiac, hepatic, renal, pulmonary diseases, diabetes mellitus, cancer, and electrical burns.
BSA, body surface area, burned.

formulas (arginine intake: 10.9 g/day,³⁴ 17 g/day,³⁵ 6.1 g/day³⁶) reduced the incidence of fistulas in patients undergoing elective surgery due to oral, laryngeal, and pharyngeal cancer compared with the control group that received an arginine-free formula. However, the incidence of wound infections was not different between the groups.^{34–36} A similar study of the same working group found less fistulas postoperatively in patients who received 20 g arginine by an enteral formula compared with patients who received only 12.3 g arginine, suggesting beneficial effects from formulas that were highly enriched with arginine.³⁷ Meta-analyses of RCT have shown that enteral formulas (e.g., Impact®; Novartis Nutrition, Stresson®; Nutrica) with a variety of immunomodulatory nutrients (arginine, long-chain omega-3 fatty acids, and ribonucleic acids) lower the incidence of several wound-healing complications of infections (fistula, anastomosis, and incision dehiscence)³⁸ and the incidence of anastomotic dehiscence in patients with gastrointestinal malignancy undergoing elective surgery.³⁹

Glutamine supplementation (1.0 g/kg body weight [BW]/day, 6 days before and 5 days after surgery) to patients with colorectal cancer undergoing surgery reduced the incidence of wound complications (wound infection, wound dehiscence, and intraabdominal abscess) compared with the control group without glutamine infusion.⁴⁰ An RCT of my own working group has recently shown that the supplementation of glutamine in combination with antioxidant micronutrients by an ONS (Glutamine Plus®; Fresenius-Kabi) decreased the time to wound closure in trauma patients suffering from disorders in wound healing compared with patients who received maltodextrine as placebo. Vascular growth factor-A in serum, wound temperature, as well as relative hemoglobin, blood flow, and blood velocity at 2 mm tissue depth of the wound did not change. However, a decrease in oxygen saturation, observed in the placebo group, did not occur in the verum group.⁴¹

Treatment of burns

Three RCT investigated the impact of glutamine supplementation in patients with severe burns (Table 4).^{42–44} Zhou *et al.* used an enteral formulation (Ensure®; Abbott) enriched with glutamine (0.35 g glutamine/kg BW/day; Ajinomoto).⁴² Peng *et al.* provided 0.5 g glutamine (verum) or glycine (placebo) per kg BW to patients fed with an oral or enteral diet that was rich in protein (2.0 g/kg BW/day) and energy (180 kJ/kg BW/day).⁴³ In both trials, the rate of wound healing was higher in glutamine-supplemented patients compared with

controls.^{42,43} Pattanshetti *et al.* fed an isonitrogenous enteral formula that was also enriched with glutamine (0.5 g/kg BW/day) (verum) or not (control). Wounds healed faster in the verum than in the control group.⁴⁴ Thus, glutamine supplementation (0.35–0.5 g/kg BW/day) supports the healing of burns.

Berger *et al.* showed that a saline solution enriched with trace elements (mean daily intake 22 mg zinc, 90 µg selenium, and 2.7 mg copper) improved the healing in adults with severe burns compared with patients who received a saline solution without trace elements (placebo), with regard to the lower grafting requirements.⁴⁵ In a double-blind, placebo-controlled trial with burned children, wound closure was accelerated by supplementation of ascorbic acid, α -tocopherol, and zinc. The given dose was dependent on age (mean daily intake: 900 mg ascorbic acid, 400 mg α -tocopherol, and 7 mg zinc) (Table 4).⁴⁶

DISCUSSION

Wound healing is a hypermetabolic and catabolic state with an increased requirement in energy, protein, selected micronutrients, and an increased requirement in arginine and glutamine.^{2,3} Hence, an increased supply of energy and selected nutrients may improve wound healing. Considering the socioeconomic burden for the therapy of wound-healing complications after surgery and for the healing of chronic wounds,⁹ dietary supplements designed for the healing of acute wounds and for the prevention and treatment of chronic wounds are of great interest in wound care. The aim of this review was to evaluate the efficacy of supplements that should improve wound healing.

Actually, there is no evidence for a beneficial effect of zinc for the treatment of arterial and venous leg ulcers.¹² This is plausible, as these wounds are caused by venous insufficiency, varicosis, and macroangiopathy that have to be treated. Since 75–85% of total plasma zinc is bound to albumin⁴⁷ for which a deficiency could be observed in almost 30% of patients with venous leg ulcers,⁴⁸ the lacking evidence for a beneficial effect of zinc treatment on ulcer healing may be due to a deficiency in albumin. Considering that patients with venous leg ulcer suffer from inflammation,⁴⁸ a phenomenon associated with low serum albumin,⁴⁹ low albumin levels may not necessarily reflect a dietary protein deficiency. Nevertheless, an adequate protein intake may be a prerequisite for improving leg ulcer healing by the supplementation of zinc.

The results from intervention studies on the impact of dietary supplements on prevention of PU

are divergent (Table 1). The reasons remain speculative, as data on the dose of ingested micronutrients, and on total energy and protein intake from diet and supplement are sometimes lacking.^{14,16} Nevertheless, formulations that are rich in energy and protein, also providing micronutrients such as ascorbic acid and zinc, may be helpful for PU prevention.

For PU treatment, however, evidence exists from RCT for a beneficial effect of protein-rich supplements providing large amounts of ascorbic acid (475–569 mg), zinc (17–30 mg), and arginine (5.7–9 g).^{20–22} This confirms earlier recommendations that supplementation of vitamin C in doses about 500 mg, combined with at least 17 mg zinc, seems to be necessary for therapeutic effects on wound healing, maybe in combination with arginine.⁵⁰ The European Pressure Ulcer Advisory Panel and the National Pressure Ulcer Advisory Panel recommend a protein intake of 1.25–1.5 g/kg BW/day.⁵¹ A recently published trial on nitrogen balance found an average protein requirement of 0.95 g/kg BW/day in patients with PU, with a range of 0.7–1.3 g/kg BW/day, dependent on wound area and exudate volume.⁵² Considering the increased protein requirement in patients with PU healing, ONS enriched with protein should be preferred to protein-free products.

In healthy subjects, high-dose supplementation of zinc (150 mg/day)²⁹ and ascorbic acid (>1,000 mg/day) along with pantothenic acid (>200 mg/day)^{30,31} has shown to improve the healing of surgical wounds in healthy subjects. Since data are scarce, evidence for beneficial effects is actually low.

Arginine supplementation did not affect wound healing in patients undergoing autografting as a part of reconstructive surgery,^{32,33} but lowered the risk for fistulas in patients with oral and laryngeal cancer undergoing elective surgery.^{34–37} The different effect on wound healing may be explained not only by the choice of parameters, but also by the health status of the participants, which was probably much worse in cancer patients than in patients with reconstructive surgery. Since formulations for immunonutrition enriched with arginine, omega-3-fatty acids, and ribonucleic acids lower the risk of several wound complications (fistula, anastomosis, and incision dehiscence) and also the risk of anastomotic dehiscence,³⁸ these formulations seem to be more efficient for wound healing in critically ill patients than products providing exclusively arginine. Since isolated glutamine⁴⁰ as well as glutamine-enriched ONS,

TAKE-HOME MESSAGES

- ONS or enteral formulations providing arginine and selected micronutrients such as vitamin C and zinc efficiently support PU healing.
- High-dose supplementation of zinc, vitamin C, and pantothenic acid in addition to a regular diet may support the healing of surgical wounds in healthy subjects.
- Formulations with the label “immunonutrition” providing arginine and further immunomodulatory nutrients lower the risk of several wound complications in critically ill patients undergoing surgery.
- Formulations enriched with glutamine and antioxidant micronutrients may support the healing of traumatic wounds and can improve the healing of burns.

providing also antioxidant micronutrients⁴¹, have shown beneficial effects on wound healing, combined supplementation of glutamine with a range of micronutrients such as vitamin C E, β -carotene, zinc, and selenium seems to be reasonable for the treatment of surgical or traumatic wounds in critically ill patients.

Glutamine in doses of 0.35 g/kg BW/day⁴² and 0.5 g/kg BW/day,^{43,44} respectively, improved the healing of burns in each trial (Table 4); glutamine is an efficient tool in the treatment of burns. Since supplementation of selenium, zinc, and copper⁴⁵ and of vitamin C, vitamin E, and zinc⁴⁶ also support the healing of burns, combined supplementation of glutamine with selenium, zinc, copper, and vitamins C and E may provide additive or even synergistic effects in the healing of burns.

CONCLUSION

In conclusion, commercially available supplements, rich in protein, ascorbic acid, zinc, and arginine, are efficient tools for PU healing. Evidence for beneficial effects on the healing of surgical wounds by high-dose supplementation of zinc, ascorbic acid, and pantothenic acid in healthy subjects is low. However, formulations enriched with arginine, n-3-fatty acids, and ribonucleic acids lower the risk of several wound complications and the risk of anastomotic dehiscence. These formulations should be recommended for critically ill patients with cancer undergoing elective surgery. Formulations providing glutamine and antioxidant micronutrients may be useful for the treatment of traumatic wounds and are efficient for the healing of burns.

AUTHOR DISCLOSURE AND GHOSTWRITING STATEMENT

No conflicts of interest exist. The author assures the writing of this article solely.

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