Effectiveness of Arginine Supplementation on Wound Healing in Older Adults in Acute and Chronic Settings: A Systematic Review

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ABSTRACT

OBJECTIVE: To examine the effect of arginine supplementation on wound healing, as measured by wound size and healing rate, in older adults in acute and long-term care (LTC) settings.

DATA SOURCES: PubMed, CINAHL Plus, Google Scholar, and OpenGrey databases.

STUDY SELECTION: Randomized clinical trials and clinical studies were considered for this review. Selection criteria included English-language articles published after 2008 that provide data on older adults with pressure injury receiving arginine supplementation in acute care and LTC settings.

DATA EXTRACTION: Data were extracted from the articles using a predefined checklist including study size and design, participant characteristics (age, pressure injury stage, relevant comorbidities), nutrition intervention and dosage, duration of study, outcomes, and publication year. Studies were appraised using the National Institutes of Health's Quality Assessment of Controlled Intervention Studies tool.

DATA SYNTHESIS: A preliminary search yielded 39 articles after removing duplicates. Abstracts and titles of articles were screened, and 23 full-text articles were examined further. Ultimately, six articles met the inclusion criteria.

CONCLUSIONS: Current evidence suggests that arginine supplementation in conjunction with oral nutrition supplementation may promote wound healing in older adult patients in acute care and LTC settings as evidenced by significant reductions in wound size and improvements in wound healing when compared with oral nutrition supplementation alone. A definitive conclusion about the use of arginine supplementation alone to promote wound healing cannot be drawn because of limitations in the available literature. Additional high-quality studies are needed to examine arginine supplementation alone as a potential therapy for PI.

KEYWORDS: acute care, arginine, long-term care, nutrition, nutrition supplementation, older adults, pressure injury, supplementation, systematic review, wound healing

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INTRODUCTION

Pressure injuries (PIs) are of clinical concern to healthcare professionals in acute and long-term care (LTC) facilities because of their impact on survival, quality of life, and medical cost.[1] Pressure injuries are common in hospitalized patients and older adults in LTC. In the US, 2.5 million patients develop PIs every year in hospitals, with a national incidence rate of 4.5%, and in LTC facilities, about 7.48% of residents had PIs in the first quarter of 2017.[1,2]

Cases of PI affect not only quality of life but also length of stay, healthcare costs, and patient outcomes.[1] The National Medicare Patient Safety Monitoring System Study found that lengths of stay were almost 7 days longer for patients with PIs (11.2 days) compared with patients without PIs (4.8 days).[1] Further, a nationwide study found that there was a $19,300 increase in hospital charges for patients with PIs ($36,500 total cost) compared with those without ($17,200 total cost) and that the cost of PI management in the US healthcare system was more than $9.1 billion a year.[3] The study concluded that patients with PIs had significantly higher mortality than those without.[3]

The National Pressure Ulcer Advisory Panel (NPUAP) defines a PI as "localized damage to the skin and underlying soft tissue usually over a bony prominence or related to a medical or other device."[4] Pressure injuries are staged from 1 to 4, depending on the severity of the damage to skin and tissue, with stage 4 being the most severe.[4] They are common in clinical settings, such as hospitals or LTC facilities, where patients and residents are more likely to have risk factors that promote skin breakdown. Risk factors for PI include limited mobility because of physical or cognitive impairment, advanced age, urinary incontinence, edema, malnutrition, diabetes mellitus, peripheral vascular disease, obesity, and cardiovascular disease.[4] Malnutrition has also been significantly associated with the development of PIs in patients who are hospitalized.[5]

In healthcare facilities, prevention and treatment protocols for PI include the use of risk assessment tools, support surfaces, repositioning, skin care, and frequent toileting.[6] Current guidelines from the NPUAP include recommendations for nutrition interventions

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to both prevent and treat PI. Guidelines include nutrition screening at admission, adequate intake of energy and protein based on patient's body weight (30–35 kcal/kg body weight and 1.25–1.5 g protein/kg body weight for adults), and proper hydration to promote wound healing for those with existing PIs.[7] These guidelines also recommend fortified foods, oral nutrition supplements (ONSs), and vitamin and mineral supplements for individuals who are not achieving adequate dietary intake. However, there are currently no specific recommendations regarding dosage of micronutrient supplementation for wound healing.[7]

Effective treatment of PIs is essential to improve patients' quality of life and reduce healthcare costs. In 2008, the CMS announced that it will no longer pay for additional costs of hospital-acquired PIs, leaving healthcare facilities with further responsibility to improve PI prevention and treatment to mitigate the cost of PI complications. Nutrition supplementation, in conjunction with skin care and nursing protocols, is one avenue for treatment of PIs that necessitates further research. Despite the importance of nutrition supplementation in promoting wound healing in patients with PIs, limited research has been done in this area. Accordingly, there is a need for randomized controlled trials (RCTs) on this topic to guide clinicians in applying evidence-based practices.

Micronutrients such as vitamin A, vitamin C, and zinc have been studied in relationship to wound healing, with a body of evidence suggesting that they may be beneficial in individuals with PIs who are at risk of nutrition deficiency.[7] Arginine is an amino acid that has also been studied, but formal recommendations have not been developed for supplementation in those with PIs. When nutrition requirements cannot be met with traditional high-calorie and protein supplements, current guidelines recommend supplementing with high protein, arginine, and micronutrients for adults with a stage 3 or 4 PI.[7] These guidelines do not recommend a dosage or duration of supplementation.

Arginine plays a role in protein synthesis; it is needed to promote cell division, immune function, and hormone release.[8] It stimulates T-cell responsiveness, helping to prent infection and promoting wound healing.[9] Healthy individuals can obtain their required arginine from diet alone; however, individuals under stress (such as during burn recovery, injury, or sepsis) require more arginine, making it a conditionally essential amino acid.[10] An essential amino acid cannot be synthesized by the body and must be obtained from the diet. Nitric oxide has vasodilatory, antibacterial, and angiogenic properties that may facilitate wound healing.[10] Because arginine is a biologic precursor for nitric oxide, it has been proposed that arginine supplementation may aid in wound healing by enhancing nitric oxide production.

This systematic review aims to provide a current overview of the impact of arginine supplementation on wound healing and wound size in older adults in acute care and LTC settings. Reviewing RCTs and clinical studies on the use of arginine supplementation for the promotion of wound healing will assist clinicians in decision-making and guide clinical practice.

METHODS

Literature Search

A comprehensive search was conducted on PubMed, CINAHL Plus, Google Scholar, OpenGrey (for gray literature), the Cochrane Central Register of Controlled Trials (CENTRAL), and EndNote in September and October 2018 to identify relevant articles and reviews related to arginine supplementation for the promotion of wound healing. Search terms included arginine AND wound healing AND (elderly OR geriatric), arginine supplement* AND pressure injury. Reference lists of potential eligible articles and literature reviews were also examined for potential articles.

Selection Criteria

A reviewer screened titles and abstracts identified from the initial literature search for inclusion in this review. Potentially relevant articles were screened using predefined inclusion criteria (Table 1). Titles and abstracts that did not meet the inclusion criteria were excluded, and the full texts of the remaining potentially relevant articles were obtained and assessed.

Data Extraction

A standardized data extraction form was used to record the following information regarding each study included in this review: authors, year of publication, study size and design, participant characteristics (age, wound type and PI stage, relevant comorbidities), nutrition intervention, arginine dosage, duration of study, adverse events, and outcomes.

Risk of Bias in Individual Studies

The methodological and reporting quality of each included study was assessed by a single reviewer using the National Institutes of Health's Quality Assessment of Controlled Intervention Studies tool. There are 14 questions in the tool, which is designed to help

Table 1.

INCLUSION CRITERIA

- Randomized controlled trial and/or clinical trial
- Peer-reviewed
- English language
- Published since 2008
- Older adult population in either acute or long-term care healthcare settings
- Study duration of 3 wk or longer
- Studies using supplements containing arginine
- Primary outcome of wound healing as measured using the Pressure Ulcer Scale for Healing tool or change in wound size

reviewers identify potential risk for bias that could bring into question the validity of the study. The questions on this assessment tool allow reviewers to focus on key concepts to evaluate a study's internal validity.

RESULTS

Study Selection

The initial literature search yielded 65 potentially relevant articles. After removal of duplicates, 39 articles were assessed for inclusion in this review; 17 were excluded based on title and abstract. Twenty-three full-text articles were considered for inclusion, and six studies were selected for final inclusion.[11–16] A flowchart outlining the selection process is shown in the Figure. Three of the studies included in this review were conducted in LTC settings,[11,13,15] and two were conducted in acute care facilities.[12,14] Participants in the final study were in either acute care or LTC settings.[16] The six articles provide insight into the role of arginine supplementation on wound healing or wound size in 572 older adult participants with PIs in acute care and LTC settings.[11–16]

Outcome Measures of Included Studies

All six studies included in this review measured either wound healing rate or wound size as an outcome to determine the effect of arginine supplementation on PI healing. A common tool for assessing wound healing is the Pressure Ulcer Scale for Healing (PUSH) tool, which was designed by the NPUAP.[17] The PUSH tool was used in all studies included in this review to measure wound healing. This tool is frequently used in healthcare facilities because of its accuracy and speed in measuring wound status over time. The PUSH tool uses three parameters: wound size (greatest length × greatest width = wound surface area), exudate amount, and tissue type (to indicate healing). A score of 0 indicates that the wound is healed.[17] Studies using this tool assess change in PUSH score to measure the rate of wound healing.[17]

Wound size is a strong indicator of healing status because wounds decrease in area as they heal.[18] It is determined by measuring length, width, and depth of the wound in centimeters.[18] This measurement is a component of the PUSH tool but is used as the primary outcome in some of the studies included in this review.[17]

Characteristics of Included Studies

A summary of study characteristics is shown in Table 2. Of the six studies included in this review,[11–16] one was an open trial in which participants were not randomized and was not placebo-controlled.[11] All of the other studies were RCTs.[12–16] Of the five RCTs, all but one included a control group.[13–16] The one RCT without a control group compared outcomes with historic data, essentially using these data as a control.[12] All studies used an ONS with protein and arginine; all but one used an ONS enriched with other nutrients in addition to arginine.[11–13,15,16] Nutrients included in supplementation varied from study to study, but

Figure.
STUDY SELECTION DIAGRAM

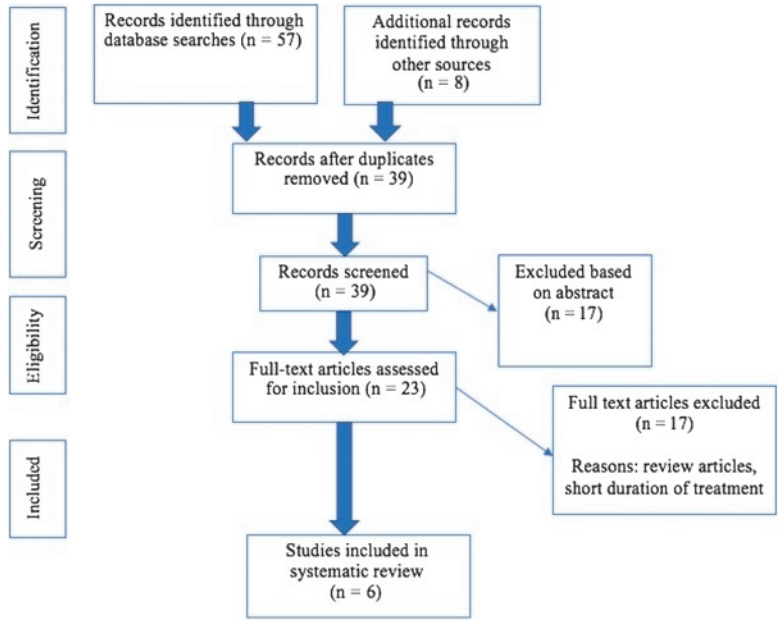

Table 2.

SUMMARY OF INCLUDED ARTICLES

Author	Sample Size (Treatment, Control)	Duration, wk	Oral Nutrition Supplement	Treatment Frequency	Setting	Wound Type	Quality Assessment Score	Results
Cereda et al[13]	n = 13, n = 15	12	34 g protein 6 g arginine 500 mg vitamin C 18 mg zinc	Daily	LTC	Stage 2–4 PI	12	Reduction in Pressure Ulcer Scale for Healing score in treatment group, $P < .001$
Bauer et al[14]	n = 12, n = 12	8	10.5 g protein 4.5 g arginine	Twice daily	Acute care facility	Chronic wounds	11	Reduction in Pressure Ulcer Scale for Healing score in control group, $P = .044$
Cereda et al[15]	n = 101, n = 99	8	10 g protein 1.5 g arginine 4.5 g zinc 19 mg vitamin E 125 mg vitamin C	Four times daily	LTC	Stage 2–4 PI	13	Reduction in PI area in treatment group, $P = .018$
Heyman et al[11]	n = 245	9	20 g protein 3 g arginine 250 mg vitamin C 38 mg vitamin E 9 mg zinc	Three times daily	LTC	Stage 2–4 PI	7	Reduction in PI area in treatment group, $P = .0001$
Leigh et al[12]	n = 23	3	4.5 g arginine 155 mg vitamin C 40.5 mg vitamin E OR 9 g arginine 310 mg vitamin C 81 mg vitamin E	Once daily	Acute care facility	Stage 2–4 PI	14	Improvement in wound healing in both treatment groups compared with historical control; no difference in healing between treatment groups; $P < .001$, $P = .991$
Van Anholt et al[16]	n = 22, n = 21	8	20 g protein 3 g arginine 238 mg vitamin E 250 mg vitamin C 38 mg vitamin E 9 mg zinc	Three times daily	Acute care or LTC	Stage 3–4 PI	12	Reduction in PI area in treatment group; $P \leq .016$

Abbreviations: LTC, long-term care setting; PI, pressure injury.

most frequently included zinc, vitamin C, vitamin E, and vitamin A. Arginine dosage ranged from 4.5 to 9 g total per day across studies, with participants commonly taking multiple servings daily.[11–16] Three studies provided 9 g of arginine total per day as a treatment.[11,14,16] Study durations ranged from 3 to 12 weeks, with 8 weeks being the most common duration.[11–16]

Wound Healing and Wound Size Results

Five studies found a significant improvement in either wound healing or wound size following supplementation with ONSs enriched with arginine.[11–13,15,16] Two of these studies found a significant improvement in wound healing rate in the treatment group as measured by PUSH score.[12,13] Three studies found a significant decrease in wound size in the treatment group compared with the control group following arginine supplementation.[11,15,16] Improvement in wound healing rate and wound size was seen in as little as 3 weeks of arginine supplementation in one study.[12]

Only one study, by Bauer et al,[14] found a significant improvement in wound healing in the control group compared with the treatment group. In this study, participants received either a standard ONS containing 9 g of protein and 1,050 kJ (251 calories) or a wound-specific ONS containing 10.5 g of protein, 1,050 kJ (251 calories), and 4.5 g of L-arginine twice daily for 4 weeks, with ongoing wound and nutrition care for an additional 4 weeks.

Strengths and Weaknesses of Included Studies

All studies included in this systematic review were evaluated for quality using the National Institutes of Health's Quality Assessment of Controlled Intervention Studies tool. Five studies scored 10 points or higher, indicating a high-quality study.[12–16] One study scored 7 points, indicating a moderate-quality study.[11] No studies included in this review received a score indicating low quality.

The open trial study discussed previously scored lowest on the quality assessment tool, indicating moderate quality and highlighting

potential risk for bias.[11] This is because the study was not controlled or blinded. Further, different clinicians conducted wound measurements and wound grading at the beginning and end of the study, which could lead to measurement bias and potentially skew results. This study did not use exclusion criteria and included participants with multiple comorbidities, such as diabetes mellitus. These comorbidities may have affected the rate of wound healing and thus the results. In comparison, four of the other studies included in this review excluded participants with comorbidities that may affect wound healing, such as those with diabetic ulcers, infection, or peripheral vascular disease.[12,13,15,16]

The study by Bauer et al[14] also had several limitations. Researchers included patients with comorbidities such as diabetes and obesity, which may affect wound healing rate.[14] Patients and clinicians in this study were not blinded as to whether the participants belonged to the treatment or control group because of the open label on the ONSs, leading to a possibility of the placebo effect; however, the nurse wound specialist who measured wound healing using the PUSH tool was blinded to which patients were receiving arginine supplementation. Further, even though there were no significant differences in baseline characteristics of the control and treatment groups in this study, 92% of patients in the treatment group had diabetic ulcers, compared with 67% in the control group, introducing a possible selection bias. Diabetic ulcers may heal at a different rate than a PI, which may affect outcomes in this study. This study had a small population (N = 24) and was the only one included in this review that used an ONS with only protein, calories, and arginine alone (all other studies used an ONS with protein, calories, arginine, and other micronutrients).[14] Further, it was the only one that studied participants with diabetic ulcers and chronic surgical wounds as well as PI. All other studies reviewed only participants with PIs. It is unclear whether participants with PIs had a different rate of healing than the others.

Most studies included in this review had a small study population, which limits the strength of these studies; four of the six had fewer than 50 participants.[12–14,16] Of the two studies with 200 participants or more, both concluded that there was a significant reduction in PI size following arginine supplementation compared with the control group.[11,15] However, one of these studies scored moderate on the Quality Assessment scale and had more limitations than the other studies.[11] The other study, by Cereda et al,[15] had a low risk for bias, including only participants without comorbidities that may affect wound healing such as diabetes, peripheral vascular disease, obesity, and infection.[15] The ONSs used by Cereda et al[15] had protein and calorie content in both the treatment and the control groups, with the only difference being the addition of arginine, zinc, vitamin E, and vitamin C in the ONSs provided to the treatment group.[15] It should be noted that this study included participants who were malnourished (defined by a low body mass index, recent unintentional weight loss, low serum albumin levels, or reduced food intake), whereas the other studies did not.

Only one study reported a high number of adverse events.[16] These were most commonly related to gastrointestinal issues, including nausea, diarrhea, and vomiting following ONS intake. Because of these adverse events, there was a high dropout rate in this study, with a 22.7% and 28.6% dropout rate in the treatment and control groups, respectively.[16]

All studies included in this review had a high adherence to treatment and control,[11–16] but the study by van Anholt et al[16] saw greater adherence in the control group. Despite this, researchers still found that supplementation with an arginine-enriched ONSs resulted in decreased PI size compared with the control group.[16]

Almost all treatment groups in the included studies received an ONS containing other vitamins and minerals along with arginine.[11–13,15,16] These other nutrients may be confounders that affect wound healing rate and size, independently or in conjunction with arginine. Only one study by Bauer et al[14] used arginine supplementation alone.[14] This was the only case in which the control group receiving standard ONSs had a significant improvement in wound healing compared with the treatment group. Again, this study was conducted with individuals with chronic wounds, including diabetic ulcers and surgical wounds, which may heal at a different rate than PIs.[14]

DISCUSSION

The purpose of this systematic review was to assess the effect of arginine supplementation on wound healing in older adults with PIs in acute care and LTC facilities. Five studies included in this review reported a significant improvement in wound healing in those receiving an ONS enriched with arginine as measured by wound healing rate or wound size.

Pressure injuries affect patients' survival, quality of life, and medical costs and are an area of concern to healthcare professionals. Since the CMS announcement that the cost of treating hospital-acquired PIs would not be covered, research on the prevention and treatment of PIs has increased.[19] This systematic review contributes to that research by reviewing the literature on the role of arginine in wound healing. There are currently no guidelines regarding dosage and duration of specific micronutrients such as arginine in relation to wound healing.

Previous research has shown that ONSs alone are effective in reducing the incidence of PI by 25% in patients at risk of skin breakdown.[9] This systematic review indicated that arginine may be effective at promoting wound healing in older adults with existing PI when supplemented in conjunction with ONSs. Control groups in the placebo-controlled studies included in this review

were given a high-protein ONS.[13–16] Almost all ONSs contained other vitamins and minerals along with arginine. As such, it is difficult to determine if arginine supplementation alone can promote wound healing with the appropriate nursing protocols and adequate protein intake. Therefore, specific recommendations on the use of arginine supplementation alone for wound healing cannot be reached. However, it can be concluded that a high-protein ONS enriched with arginine and other nutrients is more effective at promoting wound healing than a high-protein ONS alone.

Researchers used different arginine doses in the studies included in this review, ranging from 4.5 to 9 g; therefore, no specific conclusions can be drawn regarding dosage. The study comparing a 4.5 g arginine dose with a 9 g arginine dose found no difference in healing rate between groups.[12] This indicates that the effectiveness of arginine is not dose-dependent.

It may be relevant that the only study that supplemented arginine without adding other micronutrients was also the only study to find that the treatment group did not have a significant improvement in wound healing or wound size. This may suggest that arginine supplementation is only effective when used in conjunction with other micronutrients necessary for wound healing, such as vitamin C or zinc. It could also indicate that arginine supplementation is not necessary to promote wound healing and that the other nutrients included in the ONS were confounding variables responsible for noted improvement.

Further research on this topic is needed to determine the exact role of arginine in wound healing. Clinical RCTs that focus on a large population of study would contribute to this body of research. Homogeneous studies with participants sharing similar wounds and medical histories that exclude comorbidities that affect wound healing are needed. Studies focusing on arginine supplementation alone will help determine whether arginine supplementation is truly effective in promoting wound healing, as opposed to the other nutrients in the ONS. This will also help to determine whether the arginine dose affects wound healing.

CONCLUSIONS

Current literature suggests that arginine supplementation concurrent with ONS may promote wound healing as evidenced by increased wound healing (based on PUSH score) and decreased wound size. Five of six studies included in this review found a significant improvement in wound healing following arginine intervention as measured by wound size or wound healing rate. All three studies that included an outcome of wound size showed a significant decrease following treatment with arginine. The effectiveness of arginine is not dose-dependent; even a dose as small as 4.5 g led to an improvement in healing. Improvements in wound healing rate and wound size were seen in as little as 3 weeks of arginine supplementation.[12] Further research is recommended to reinforce these findings.

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