# Arginine: What You Need to Know for Pressure Injury Healing

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**GENERAL PURPOSE:** To provide information about arginine, its metabolism, and its role in acute and chronic wound healing, to assist providers in understanding the recommendations for arginine supplementation.

**TARGET AUDIENCE:** This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

**LEARNING OBJECTIVES/OUTCOMES:** After participating in this educational activity, the participant will:

1. Describe the characteristics of arginine.
2. Choose the metabolic processes that define arginine's role in wound healing.
3. Identify the average daily intake of arginine in an American diet.
4. Select the evidence that demonstrates the effectiveness of arginine supplementation for wound healing.

**ABSTRACT**

Nutrition has an important and integral role in wound healing. Arginine, a type of indispensable amino acid, has long been thought to have wound healing properties. The 2019 international guideline by the European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel, and Pan Pacific Pressure Injury Alliance recommends use of a high-protein, high-calorie oral nutrition supplement fortified with arginine and other antioxidants to treat adults with stage 2 or greater pressure injury and who are malnourished or at risk of malnutrition to foster healing. This article provides necessary background on this conditionally indispensable amino acid, its metabolism, and its role in acute and chronic wound healing to assist providers in understanding the recommendation for arginine supplementation.

**KEYWORDS:** amino acid, arginine, malnutrition, nutrition, pressure injury, supplement, wound healing

ADV SKIN WOUND CARE 2021;34:630–6.
DOI: 10.1097/01.ASW.0000795900.25030.5e

## INTRODUCTION

The National Pressure Injury Advisory Panel (NPIAP) defines a pressure injury (PI) as localized damage to the skin and underlying soft tissue because of intense or prolonged pressure. A PI usually occurs over a bony prominence but can also form under a (medical) device or on tissue where a device was present. Shear in combination with pressure can also cause a PI, and factors such as microclimate, nutrition, perfusion, comorbid conditions, and condition of the soft tissue can contribute.[1,2] Between 2006 and 2015, PIs affected 8.8% of the patient population in acute care, 28.8% of those in long-term acute care, 11.3% in long-term care, and 11% in rehabilitation centers.[3] Hospital-acquired PIs are considered adverse patient safety events with associated costs close to a staggering $27 billion annually.[4]

Nutrition plays an important role in the management and treatment of PIs.[5] The 2019 *Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice Guideline*[6] recommends that healthcare professionals "provide high-calorie, high-protein, arginine, zinc and antioxidant oral nutritional supplements or enteral formula for adults with a category/stage 2 or greater pressure injury who are malnourished or at risk of malnutrition." This is a significant departure from the previous guideline recommendations, in which arginine (among other micronutrients) was recommended only as supplementation for the treatment of stage 3 or 4 PIs.[7] Because arginine

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supplementation plays an important role in PI healing, this article will provide an overview of arginine metabolism, normal wound healing, the role of arginine and nitric oxide (NO) in wound healing, and the studies that examine arginine supplementation in regulating wound healing in humans.

## ARGININE

Amino acids are classified into *indispensable* (essential), *dispensable* (nonessential), and *conditionally indispensable* amino acids.[8,9] There are nine indispensable amino acids that cannot be synthesized by the body and must be obtained through diet. Dispensable amino acids are those that can be synthesized by the body. Six other amino acids, including arginine, are considered conditionally indispensable.[10] Here, when the body experiences illness or stress, dispensable amino acids become conditionally indispensable because the demand for them is greater than what the body can produce. Accordingly, they must be obtained from diet. Arginine is one of the conditionally indispensable amino acids that have been recommended with other nutrients to help aid wound healing.

## METABOLISM

The arginine metabolism process has an important effect on wound healing (Figure 1). Arginine ($C_6H_{14}N_4O_2$) is nitrogen-rich with four nitrogen atoms in each molecule (32% nitrogen compared with an average of 16% in other amino acids; Figure 2).[11] Arginine is primarily derived endogenously; approximately 80% is derived from body protein breakdown, 10% to 15% from endogenous de novo production in the kidneys, and the rest from dietary sources.[9] Most dietary arginine is absorbed in the jejunum of the intestine. It is then rapidly metabolized by arginase into ornithine and urea during the urea cycle in the liver. Ornithine is a substrate of polyamines that takes part in healing of damaged tissue and allows for regeneration. Ornithine synthesized in the urea cycle can be metabolized to glutamate-semialdehyde, which can serve as a precursor for pyrroline-5-carboxylate (P5C).[12,13] A P5C reductase created from the metabolism of arginine catalyzes the reduction of P5C to synthesize proline, which can support collagen synthesis, wound repair, and skin remodeling.[12–14]

Arginine biosynthesis occurs through the intestinal-renal axis where citrulline derived in the intestine from proline, glutamate, and glutamine is released into the bloodstream and metabolized primarily by the kidneys to produce arginine. Conditions such as wounds, injury, trauma, sepsis, and intestinal and renal failures can compromise arginine synthesis and bioavailability. These conditions may lead to arginine deficiency and prolong the body's time to recovery.[9]

## WOUND HEALING

Arginine is a multipurpose amino acid. It plays a vital role in wound healing (Figure 1) as a secretagogue to enhance the release of growth hormone and as a precursor to NO, proline, and polyamines. Arginine increases the production of insulin-like growth factor 1, which is an important hormone for cell growth and wound healing.[15] Sequentially, insulin-like growth factor 1 catalyzes ornithine decarboxylation to generate polyamines.[15] Polyamines are important for cell growth, proliferation, differentiation, and multiplication and are necessary for angiogenesis and wound repair.[15] Their antioxidant

**Figure 1. ARGININE METABOLISM AND ITS ULTIMATE EFFECT ON PRESSURE INJURY HEALING**

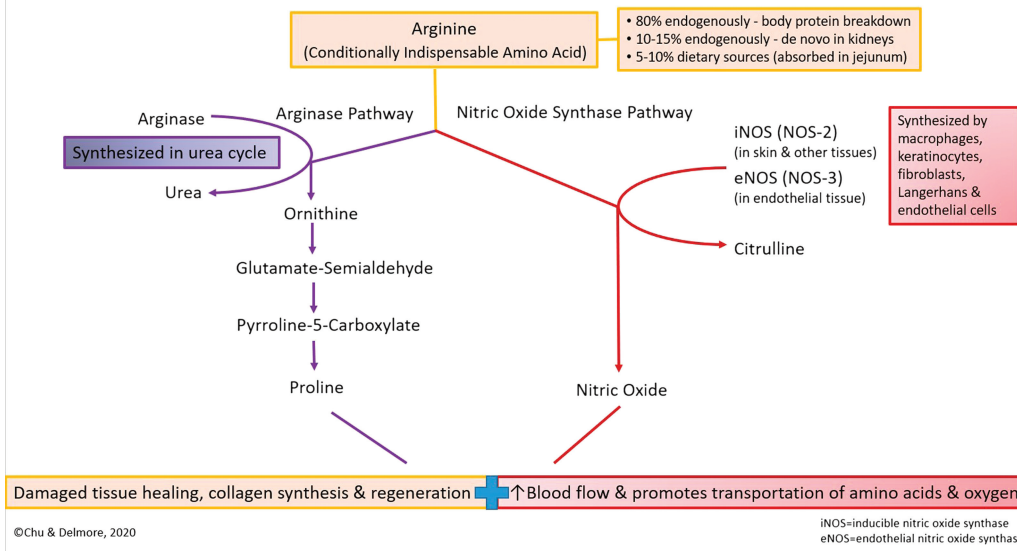
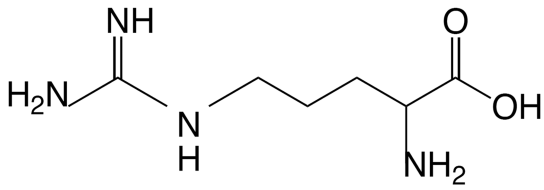


**Figure 2. CHEMICAL FORMULA OF ARGININE**




property protects cells from free radical damage associated with oxidative stress.[16]

## ARGININE AND NITRIC OXIDE

As seen in Figure 2, arginine is a precursor of NO as a substrate of NO synthase (NOS). Nitric oxide is a radical that increases blood flow and promotes the transportation of amino acids and oxygen to wounds. Synthesis of inducible NOS (iNOS) by macrophages, keratinocytes, fibroblasts, and Langerhans and endothelial cells is activated by bacteria and inflammatory cytokines and suppressed by glucocorticoids.[15] Of the three isoforms of NOS involved in NO synthesis, iNOS is located in skin, among other tissues, and endothelial NOS is primarily located in endothelial tissue. Inducible NOS is the major source of NO production in wounds. The constitutive isoforms of NOS generate low levels of NO at baseline. Their activities are regulated by the calcium-calmodulin system. Cytokines, growth factors, and inflammatory stimuli on target cells induce iNOS that results in the release of high levels of NO.[17]

## ACUTE AND CHRONIC WOUND HEALING

The amount of time each phase of wound healing takes to complete may differ or be delayed based on the patient's severity of illness and whether a wound is acute or chronic.[18–20] An acute wound proceeds through the inflammatory and proliferative phases of healing in about 21 to 30 days.[21] Partial-thickness PIs (stages 1 and 2) are considered acute wounds because they do not normally progress to more severe, chronic PI stages (stages 3 and 4, unstageable, deep tissue PI) except under mitigating circumstances.[22]

In contrast, a chronic wound is an open wound that has not healed or demonstrated significant healing after 30 or more days.[19,20,23] Chronic wounds are suspended in the inflammatory phase and cannot proceed to the next physiologic event of repair, often because of some dysfunction created by uncorrected intrinsic and/or extrinsic factors.[19,20,23,24] Until these factors are addressed and corrected, if feasible, the chronic wound cannot proceed to the proliferation phase.[19,20] Full-thickness PIs (eg, stages 3 and 4) are a type of chronic wound.

## ARGININE METABOLISM IN WOUND HEALING

Arginine is a regulator of protein expression. The two opposing pathways for arginine metabolism (NOS and arginase) regulate wound healing (Figure 3). These pathways are chronologically arranged so that the stimulation of one pathway results in suppression of the other.[15,25] Not only does arginine metabolism play a role in wound healing, but the nuances of these processes are also apparent in distinct ways in acute and chronic wound healing. In acute wounds, the normal processes of arginine and NO complement the healing process. In chronic wounds, chronicity is reflected in the malfunctions of arginine and NO.

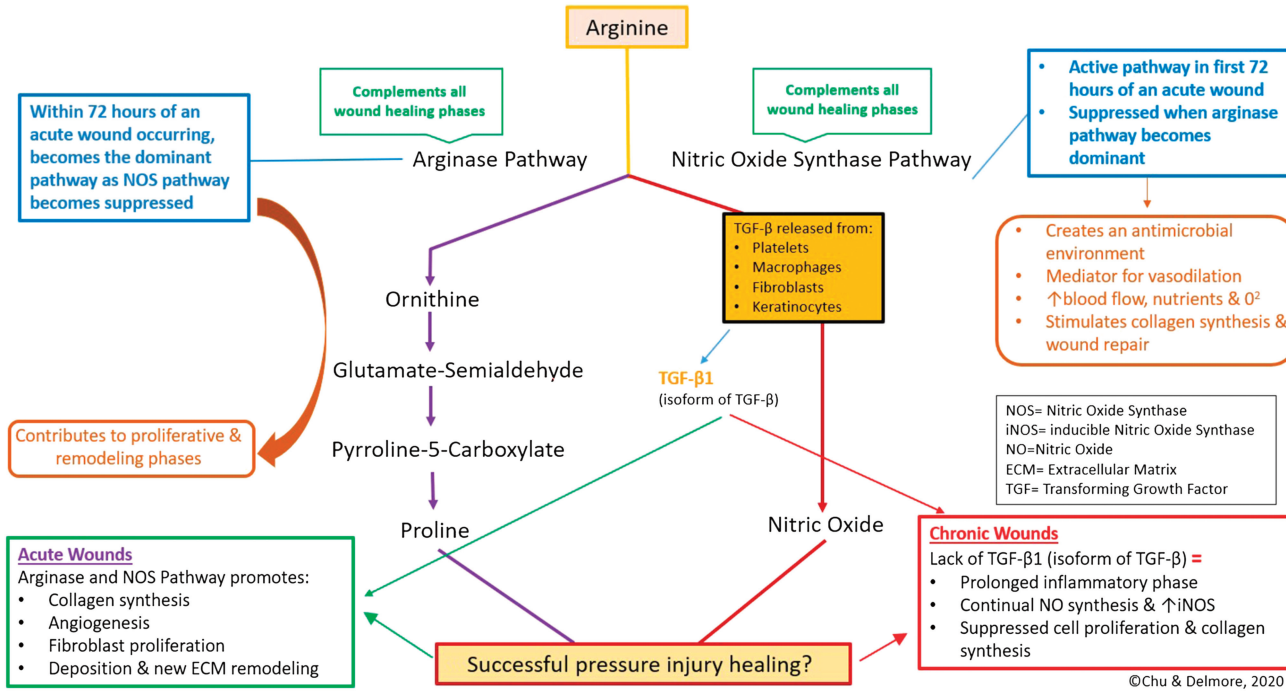
During the inflammatory phase of acute wound healing, arginine is metabolized by NOS to form NO. In the first 72 hours of an acute wound, NOS is active in the metabolism of arginine and synthesizes NO and citrulline. The iNOS is stimulated by bacteria, and the resulting NO creates a cytotoxic (antimicrobial) wound environment. In addition, NO mediates vasodilation in blood vessels that impacts circulation and increases blood flow, nutrients, and oxygen in the wound to stimulate collagen synthesis and wound repair.[15,26]

Also in the first 72 hours, the arginase pathway becomes the dominant enzyme pathway in arginine metabolism, whereas NO synthesis is suppressed. Arginine is metabolized by arginase into ornithine and urea in the fibroblasts of wounds. The result is ornithine from the metabolism of arginine via arginase I, which is a precursor of polyamines that is important for cell proliferation in wound healing. Arginase or ornithine decarboxylase inhibition exhausts the supply of polyamines and thus suspends cell growth. In contrast, the resulting ornithine from the metabolism of arginine via arginase II further metabolizes into proline and glutamate, which are important factors in collagen synthesis.[12,13] The end result is synthesis of NO and the arginase enzyme pathway becoming the predominant pathway. The end products of proline and glutamate help in P5C reduction from ornithine in the urea cycle to proline and ultimately also contribute to the proliferative and remodeling phases.[14]

In chronic wounds, the processes associated with arginine and its NO complement are affected. Normally, the profibrotic transforming growth factor β (TGF-β) can inhibit the iNOS pathway and stimulate the arginase pathway supporting collagen synthesis.[15] Suppression of the iNOS pathway by TGF-β increases the supply of arginine to be metabolized by arginase, resulting in increased synthesis of polyamines and ornithine for cell proliferation and collagen synthesis, respectively.[15] The regulatory mechanism between the two different metabolic pathways of arginine in the inflammatory and proliferation phases of wound healing promotes collagen synthesis. The TGF-β takes part in the inflammatory phase and stimulates angiogenesis, fibroblast proliferation, collagen synthesis, and deposition and remodeling of the new extracellular matrix. However, TGF-β1 is not found in chronic, nonhealing wounds, impairing healing.[27]

Although it is essential to wound healing, if NO continues to build up from the metabolism of arginine via

**Figure 3.** THE DIFFERENCES IN ARGININE METABOLISM IN ACUTE VERSUS CHRONIC WOUNDS




iNOS or NO synthesis is prolonged, the inflammatory phase in chronic wounds is equally prolonged. An elevated concentration of iNOS in chronic wounds suppresses cell proliferation, collagen synthesis, and wound closure.[15] Therefore, NO synthesis may be damaging if continued beyond the initial days of healing, resulting in a prolonged inflammatory phase. This may be the case in chronic wounds where the preferential expression of iNOS interferes with cell proliferation, collagen formation, and wound closure. It is presumed that iNOS can be suppressed when the inflammatory response is resolved or by cytokine signaling.[17]

## ARGININE SUPPLEMENTATION

The daily average dietary protein consumption of adult American men and women is 97.2 and 69.6 g, respectively.[28] Protein intake among Americans has been steady over the past decade.[29] Each gram of dietary protein is estimated to provide 54 mg of L-arginine,[15] and thus the average intake of arginine is assumed to be 4 to 5 g/d in an American diet.[30,31] That said, the arginine content of food is depleted by various cooking methods.[32,33]

In time of physiologic stress, such as during PI healing, arginine supplementation may become crucial to support cell growth and repair when dietary consumption and endogenous synthesis of arginine are inadequate.[15] Researchers have studied various populations with PIs and other wound types to determine the appropriate arginine supplementation required for acute and chronic wound healing, summarized below (full details are provided in the Table).

Although arginine supplementation has been studied in acute wounds such as surgical wounds,[34] PIs tend to be chronic (ie, stages 3 and 4). The aforementioned Clinical Practice Guideline states that arginine supplementation should be considered for stage 2 PIs, although they are considered acute, with the rationale that malnourishment or the risk of malnourishment could cause a stage 2 PI to deteriorate to a more severe PI and thus into chronicity.[6] Bauer and colleagues[35] investigated the outcome of a wound-specific oral nutrition supplement (ONS) enriched with arginine, vitamin C, and zinc compared with a standard ONS in hospitalized patients with chronic wounds. Unexpectedly, instead of improvements in the intervention group, there was a significant improvement in the Pressure Ulcer Scale for Healing (PUSH) score in the standard ONS group. The authors concluded that standard ONSs may be more effective in supporting wound healing than a wound-specific formula in hospitalized patients.

Several studies in the long-term care setting had significant findings. Heyman and collegues[36] examined the effects of a wound-specific ONS on PI healing in a nursing home population. They found that after 9 weeks of supplementation, the mean PI area and exudate amount were significantly reduced. They concluded that standard care supplemented with a wound-specific high-protein ONS reduced average PI area. Cereda and colleagues[37] evaluated whether supplementation with arginine,

**Table. SUMMARY OF RESEARCH STUDYING THE EFFECTS OF ARGININE SUPPLEMENTATION ON WOUND HEALING**

| Author, Design (N) | Setting and Duration | Treatment and Frequency | Control | Wound Type | Measurement | Limitations |
|---|---|---|---|---|---|---|
| Bauer et al,[35] 2013, pragmatic RCT (24) | AC, 8 wk | 10.5 g protein<br>4.5 g arginine<br>BID | Standard ONS | Chronic wounds | PUSH score<br>QOL<br>Energy and protein intake<br>PG-SGA | Inclusion criteria: DM and obesity<br>Small sample |
| Cereda et al,[37] 2015, blinded RCT (200) | LTC, 8 wk | 20 g protein<br>3 g arginine<br>9 mg zinc<br>38 mg vitamin E<br>250 mg vitamin C<br>BID | Isocaloric, isonitrogenous standard ONS | Stage 2–4 PIs | PI area<br>Visitrak wound measurement system | Inclusion criteria: malnourished, LTC/home care patient, can drink supplements |
| Cereda et al,[38] 2017, systematic review and meta-analysis (273) | AC and LTC, 8–12 wk | Varied<br>BID to TID | Varied | Stage 2–4 PIs | PI area | Limited no. of studies<br>Most available studies did not consider support until complete healing (secondary outcome measure)<br>Underpowered trials |
| Cereda et al,[42] 2017, economic analysis (138) | LTC, 8 wk | 250 kcal<br>20 g protein<br>(15% arginine)<br>BID | Isocaloric, isonitrogenous standard ONS<br>250 kcal<br>20 g protein | Stage 2–4 PIs | Difference in cost | No info on economic impact of high-quality nutrition care vs no intervention<br>Not focused on indirect costs<br>Local healthcare system perspective only<br>Primary end point did not include economic value of disease-specific nutrition intervention |
| Heyman et al,[36] 2008, open trial (245) | LTC, 9 wk | 20 g protein<br>3 g arginine<br>9 mg zinc<br>38 mg vitamin E<br>250 mg vitamin C<br>TID | N/A | Stage 2–4 PIs | PI area<br>Exudate amount | Open trial<br>Interrater reliability between centers not assured<br>No objective exudate measurement<br>PI area measured by ruler rather than planimetry |
| Leigh et al,[41] 2012, RCT (23) | AC, 3 wk | 4.5 g arginine<br>155 mg vitamin C<br>40.5 mg vitamin E<br>QD | 9 g arginine<br>310 mg vitamin C<br>81 mg vitamin E | Stage 2–4 PIs | PUSH score<br>SGA | No active control group<br>Small sample<br>Healing monitored over 3 wk instead of using time-to-healing data |
| Schneider and Yahia,[39] 2019, systematic review (563) | AC and LTC, 3–12 wk | Varied<br>QD to QID | Varied | Chronic wounds<br>Stage 2–4 PIs | PI area<br>PUSH score | Small sample in most studies |
| Van Anholt et al,[40] 2010, double-blind RCT (43) | AC and LTC, 8 wk | 20 g protein<br>3 g arginine<br>9 mg zinc<br>38 mg vitamin E<br>250 mg vitamin C<br>TID | Noncaloric flavored placebo | Stage 3–4 PIs | PI area<br>PUSH score<br>Nursing time<br>No. of drugs | Small sample |

**Abbreviations:** AC, acute care; BID, twice daily; DM, diabetes mellitus; GI, gastrointestinal; IMD, immunomodulating diet; LTC, long-term care; ONS, oral nutrition supplement; PG-SGA, Patient-Generated Subjective Global Assessment; PI, pressure injury; PUSH, Pressure Ulcer Scale for Healing; QOL, quality of life; QD, daily; QID, four times daily; RCT, randomized controlled trial; SGA, Subjective Global Assessment; Sx, surgery, surgical; TID, three times daily.

zinc, and antioxidants improved PI healing in patients who were malnourished. There was a significant mean reduction in PI area in the arginine-enriched formula group within 8 weeks. In addition, a 40% or greater reduction in the wound surface area was almost twice as likely in the arginine-enriched group than control. The authors concluded that 8 weeks of arginine, zinc, and antioxidant supplementation in a high-calorie, high-protein ONS improved PI healing.

Cereda and colleagues[38] conducted a systematic review and meta-analysis to evaluate the efficacy of high-calorie, high-protein ONS or enteral nutrition support enriched with arginine, zinc, and antioxidants compared with a standard supplement in patients with PIs.[35] In the intervention group, PI area reduced significantly (by 15.7%), and a 40% or greater reduction in PI size was 1.72 times more likely than among controls. It was concluded that the use of an arginine, zinc, and antioxidant-enriched ONS and enteral nutrition support for at least 8 weeks improved PI healing. Schneider and Yahia[39] revealed similar findings while examining the effect of arginine supplementation on wound healing in older adults and concluded improvement in wound size and healing.

Van Anholt and colleagues[40] investigated the effect of a high-protein, arginine- and micronutrient-enriched ONS on PI healing among patients who were not malnourished in mixed settings (healthcare centers, hospitals, and long-term care facilities). There was a significant reduction in PI size in the intervention group after 8 weeks, and in particular, a significant decrease in PUSH scores. This group had significantly fewer dressing changes, and significantly less time was spent on dressing changes per week. The authors concluded that the high-protein, arginine- and micronutrient-enriched ONS accelerated healing rate and reduced PI severity.

Leigh and colleagues[41] investigated whether PI healing would improve with a lower dose (4.5 g) of arginine fortified in an ONS compared with the current standard of 9 g/d and found it to be equally effective in decreasing PI severity, with no difference in healing rates, as measured via PUSH scores. There was a trend toward improved wound healing among well-nourished patients who received arginine, but it was not dosage dependent. In regard to PI healing, the authors concluded that administering a lower arginine dosage (ie, one packet per day) was equally effective as the previous recommended dosage of two packets per day, potentially reducing costs.

Cost-effectiveness is an important factor in determining treatment plan. As part of the OligoElement Sore Trial in long-term and home care, Cereda and colleagues[42] examined the cost-effectiveness of using an arginine-enriched ONS as part of PI treatment. Although the arginine-enriched ONS was significantly more costly than standard care, patients in the experimental group had a significant reduction in nonnutritional PI treatment expenses, such as nursing labor and dressing materials. The total PI treatment cost was also significantly lower than in the control group, resulting in total savings of €74 (approximately $87) per patient. It was concluded that in addition to improving healing, the arginine-enriched ONS reduced the cost of local PI care.

In summary, recent studies have demonstrated significant wound healing improvement among participants who received an arginine-fortified ONS. However, most of the ONSs included in these studies were also enriched with other antioxidants, such as vitamin C, vitamin E, and zinc, which also have wound healing properties. Therefore, the Clinical Practice Guideline expands its previous recommendation to now include a bundle of high-protein, high-calorie, disease-specific ONS that contains arginine, zinc, and antioxidants for adults with a stage 2 or greater PI who are malnourished or at risk of malnutrition.[43]

## CONCLUSIONS

As a wound type, PIs require multiple interventions, especially nutritional, for successful healing. Arginine and its metabolites have powerful wound healing properties via metabolism and NO synthesis. High-level evidence supports the use of a high-protein, high-calorie ONS enriched with arginine and other antioxidants to promote wound healing. Supplementation of arginine, among other nutrients, can also provide a cost-effective approach to expedite PI healing.

## PRACTICE PEARLS

- Arginine has been shown to promote wound healing in conjunction with other micronutrients.
- Arginase and NOS pathways are active and instrumental during the different wound healing phases.
- At least 4.5 g of arginine per day in combination with other antioxidants is needed to benefit wound healing.
- Administering arginine supplementation concurrently with other micronutrients can be a cost-effective treatment in addition to standard care. ●

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