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WOUND HEALING / EXPERIMENTAL

Narrative Review

MYTHBUSTING THE EFFECT OF BCAA ON WOUND HEALING

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ABSTRACT

Nutrition plays a crucial role in the wound-healing process. Nutrition deficiencies can hinder the wound healing process and prolong the recovery period turning the wound into a chronic wound. One nutrient that is rarely discussed is BCAA (Branched Chain Amino Acid). BCAA are essential amino acids that are believed to accelerate the wound healing process. This study aims to investigate the effects of BCAA on the wound healing process. Studies have shown that BCAAs can increase serum albumin levels by preventing the formation of mRNA-PTB (Polypyrimidine Tract-Binding Protein) in liver cells, which activates and accelerates the wound healing process. Administering BCAA as a single treatment is not optimal; therefore, combined therapy with other essential amino acids is necessary. BCAAs can be administered orally, enterally, parenterally, and topically.

Keywords: *Nutrition, BCAA, Wound healing, Protein, Amino acid.*

Nutrisi memegang peranan yang sangat penting dalam proses penyembuhan luka. Kekurangan nutrisi dapat memperlambat proses penyembuhan luka dan berakibat luka menjadi luka kronis. Salah satu nutrisi yang jarang dibahas adalah BCAA *(Branched Chain Amino Acid)*. BCAA merupakan asam amino esensial berantai dan melalui beberapa penelitian dipercaya dapat mempercepat proses penyembuhan luka . Studi ini ingin mengetahui efek BCAA terhadap proses penyembuhan luka. Dari studi didapatkan BCAA dapat meningkatkan serum albumin dengan cara melalui mekanisme inhibisi dari formasi mRNA-PTB *(Polypyrimidine Tract-binding Protein)* di sel hepar sehingga dapat mengaktivasi dan mempercepat proses penyembuhan luka. Pemberian BCAA sebagai terapi tunggal tidak optimal, sehingga dibutuhkan terapi kombinasi dengan asam amino esensial lainnya. BCAA dapat diberikan secara peroral, nutrisi enteral, parenteral, dan topikal.

Kata Kunci: *Nutrisi, BCAA, Penyembuhan luka, Protein, dan Asam amino*

Conflicts of Interest Statement:
The authors listed in this manuscript declare the absence of any conflict of interest on the subject matter or materials discussed.

INTRODUCTION

Any damage to the integrity of living tissue can be considered an injury. The skin, the most significant human organ, has the primary function of protecting the organs. Maintaining the integrity of the skin and maintaining the body's optimal wound healing capacity are essential conditions for healthy survival (1). Wound healing is a complex and dynamic sequence of events. Health professionals need biochemistry, physiology, cell biology, and molecular biology knowledge to make decisions about wound care and ensure that wounds heal optimally and do not become chronic. In addition, wound care can present challenges and burdens on healthcare systems, as long-term wound care requires significant financial resources (2).

Many factors can affect wound healing, and one of them is diet. Inadequate intake or lack of essential nutrients can seriously affect wound healing (3). One well-studied role of BCAAs is their ability to increase the synthesis of albumin, a protein involved in wound healing. When serum albumin falls by ten g/L, mortality increases by 137% and morbidity by 89%, ultimately leading to inhibition of wound healing (4). BCAAs (branched chain amino acids), consisting of leucine, isoleucine, and

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valine, are essential nutrients that cannot be produced endogenously by the body and must be obtained from the diet (5). Other studies show that BCAAs positively affect wound healing in patients with diabetic ulcers (6). Due to the limited research on BCAAs, the authors are interested in the effects of BCAAs on the wound healing process. The results of this review can serve as a theoretical basis or reference for other researchers to investigate the effects of BCAAs on wound healing.

METHOD

Relevant studies published between 1984 and 2023 were identified through searches in PubMed, Cochrane, and ScienceDirect using various combinations of the following keywords: "BCAA," "wound," "healing," "nutrition," "protein," and "amino acid." Additional research papers were obtained by reviewing the reference lists of relevant publications. Studies with limited credibility and those not written in English were excluded. Data extraction was conducted based on the relevance of the information to the topic rather than following a systematic paper selection approach. For a more detailed explanation of the methodology, refer to *Table 1*.

WOUND HEALING PROCESS

Wound healing consists of three phases: inflammation and hemostasis, proliferation and maturation. Generally, the wound can take 14 to 21 days to heal. The phase of hemostasis in wound healing begins immediately after skin damage. After injury, open blood vessels activate platelets and interact with collagen to release vasoconstrictors such as thromboxane A2 and prostaglandin 2a, stimulating thrombus formation and local vasoconstriction to stop bleeding (1,7). Blood clot formation is due to the production of fibrin matrix. The fibrin matrix consists of fibrinogen, which is converted to fibrin by thrombin after tissue damage. Fibrin plays a role in forming a blood clot that helps stop bleeding and also provides a framework or platform for platelets and other reactive cells to deposit in the wound. The fibrin matrix also facilitates healing by providing the structure necessary for developing healing cells. The formation and distribution of fibrin matrix is critical for smooth and effective wound healing (7,8). Immediately after the hemostasis phase, local inflammation occurs around the wound, marking the inflammatory phase. In this phase, an inflammatory reaction occurs, involving various cells and inflammatory mediators, which clear the damaged area of debris, reduce the risk of infection, and begin regeneration of the damaged tissue. In the inflammatory phase, vasodilatation occurs, which increases blood flow to the damaged area, and leukocytes, such as neutrophils and monocytes, are directed to the site of damage to clean the damaged tissue (7).

Inflammatory mediators involved in the inflammatory phase of wound healing are prostaglandins, interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma). These various inflammatory mediators regulate the inflammatory response, facilitate inflammatory cell migration and repair, and clear damaged tissue during the inflammatory phase (8,9). IL-6 also plays a role in inducing fever and increasing the release of acute-phase reactants such as heparin. In addition, IL-6 can influence immune responses, including stimulating the proliferation of T and B cells. This indicates that IL-6 is an essential mediator of the inflammatory response in the wound-healing process (10,11). This inflammatory reaction can be characterized by classic symptoms such as redness, swelling, pain, and warmth around the wound. This phase usually lasts several days to weeks before moving into the next phase of the wound-healing process (7).

The second phase of the wound healing process is the proliferation phase. The spreading phase begins about 2-3 days after the injury and lasts about three weeks.

Table 1. Summarizing the search technique

Items	Specification
Date of search	2023.07.13
Databases	PubMed, Cochrane, and ScienceDirect
Search terms used	"BCAA", "wound", and "healing" "Branched-Chain Amino Acids", "wound", and "healing"

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Items	Specification
	"Nutrition", "wound", and "healing" "Protein", "wound", and "healing" "Amino acid", "wound", and "healing"
Timeframe	1984-2023
Inclusion and exclusion criteria	The process was applied to original research papers and reviews written in English that explore the effects of BCAA on wound healing. Articles that did not specifically address the impact of BCAA on wound healing were excluded from the analysis.
Selection proces	The research was independently conducted by FT, SNS, and GH. The data selection process involved identifying the common findings across the searches performed by all three authors.

Fibroblasts play a crucial role at this stage because they produce large amounts of type III collagen to form a temporary matrix. In addition, fibroblasts produce growth factors that stimulate epithelial cell proliferation, angiogenesis, and granulation tissue formation. Fibroblast cells can transform into myofibroblasts under the cytokine TGF-β, which promotes wound contraction (11). Angiotensin II also promotes the proliferative phase by maintaining an inflammatory response that stimulates the differentiation and proliferation of fibroblast cells. This indicates that angiotensin II has a significant anti-inflammatory effect during the proliferative phase (10).

In the regeneration phase, granulation tissue is replaced by permanent scar tissue, and collagen production continues, increasing wound adhesion's strength (2). The production of collagen continues for 4-5 weeks. Newly formed collagen initially has thin properties and lies parallel to the skin. Still, over time, this collagen is absorbed and replaced by thicker collagen accumulating along the skin's stretch lines (11). At this point, the tensile strength of the wound continues to increase along with the production of collagen, increasing from 3% in the first week to 20% in the third week. Three months after the injury, the tensile strength of the wound reaches 80% of healthy skin, but it never reaches 100% (2,3). The remodeling phase is an essential stage of the wound healing process that can lead to minimal scar tissue formation and rapid healing. Disturbances in this phase can lead to hypertrophic scars, keloids, or chronic wounds that are difficult to heal. The remodeling phase reorganizes newly deposited collagen into a structured and muscular tissue based on glycosaminoglycans and proteoglycans and is the final step in the wound healing process (11).

THE ROLE OF THE NUTRITION IN THE WOUND HEALING PROCESSS

Nutrition plays an indispensable role in the wound healing process (12). Nutrients are necessary for cell proliferation, protein synthesis, and chemotactic factors, which are also necessary for wound healing (13). Protein, carbohydrates, fats, vitamins, and minerals play an important role in ensuring that the wound healing process runs optimally, while deficiencies can hinder the process and increase the risk of chronic wounds (14, 15).

Based on their requirements in the body, nutrients can be grouped into two categories: macronutrients and micronutrients (12). Macronutrients are required in more significant amounts by the body than micronutrients, but both groups play equally important roles in wound healing (8). Protein, carbohydrates, and fats are macronutrients, while vitamins and minerals are micronutrients. (16).

Wounds put the body into a catabolic state, increasing energy demands (17). Carbohydrates are the primary source of energy in the body (16). The generated power can sustain high metabolic activity for regeneration (14). Fibroblast proliferation, one of the wound healing stages, is highly sensitive to glucose levels (12). If energy is insufficient, the healing process will be prolonged (8).

Fatty acids also play an essential role in the wound healing (18). Phospholipids are crucial components in the formation of the basement membrane of the cell, and fatty acids are one of the components of phospholipids (19). Fats are transporters of vitamins A, D, E, and K. (20) Fats also help provide subcutaneous insulation and bone protection (15). Fats are crucial for the regeneration of epidermis and skin tissue. (18). Therefore, it can be concluded

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that fats play an essential role in maintaining the skin's protective capacity.

Currently, 20 vitamins and 16 minerals are known to affect the wound healing process (12). Vitamin A is a fat-soluble vitamin (20). Vitamin A deficiency impairs collagen synthesis (21). Vitamins A and B can promote wound healing by aiding epidermal growth and re-epithelialization (22). Vitamins C and E are potent antioxidants and are known to aid collagen synthesis (23,24). Vitamin D, another fat-soluble vitamin, is essential for calcium absorption, which is vital for bone formation, supports neuromuscular function, strengthens immunity, and accelerates the wound healing (25,26). Fat-soluble vitamin K is found in various green vegetables, kiwi, meat, and eggs (27). Vitamin K is primarily required for coagulation and bone metabolism and is essential for wound healing (28).

Proteins are the primary building blocks for tissue growth and repair (29). Protein intake is important as catabolism occurs during wound healing (30). Protein deficiency affects wound healing capacity, T-cell activity, phagocytic activity, and antibody levels, prolonging the wound healing process and increasing the risk of infected wounds (12, 13).

Proteins are absorbed from the intestines in the form of amino acids (29). Different types of amino acids are known to aid in the wound healing process. Arginine is a type of amino acid that increases collagen synthesis through mechanisms such as enhancing fibroblast synthesis, promoting matric deposition, angiogenesis, regeneration, antibacterial activity, and improving blood flow by nitrate oxide synthesis (31). Glutamine can aid in wound healing by acting as an energy source, promoting cell growth, helping to produce nitric oxide, reducing C-reactive protein, and acting as an antioxidant (32). Hydroxymethylbutyrate can reduce protein degradation, enhance protein synthesis, reduce apoptosis, and promote cell growth (33).

Branched-chain amino acids (BCAAs), which include leucine, isoleucine, and valine, aid in wound healing. BCAAs are known to support protein synthesis and reduce muscle proteolysis, acting as an energy source that can be stimulated independently of liver function (6).

DISCUSSION

Branched-chain amino acids (BCAAs), especially leucine, are essential for effective wound healing (34). One of the well-studied roles of BCAAs is their ability to increase albumin synthesis. Albumin is a protein that has an established relationship with the wound healing process. A decrease in serum albumin level of 10 g/L was associated with a 137% increase in mortality, an 89% increase in morbidity, and impaired wound healing (4). Decreased serum albumin levels are also associated with a weakened immune system and delayed healing of wounds caused by infections. This is evident from white blood cell phagocytosis indicators and inflammatory reactions, especially neutrophils (35). The mechanism by which BCAAs increase albumin synthesis involves the activation of the rapamycin complex (mTOR) by its two substrates, ribosomal protein S6 kinase-1 (S6K1) and translational repressor initiation factor (eIF) 4E-binding protein 1 (4E-BP1) in the liver to start the process of translation and synthesis of proteins (36). Leucine can increase albumin synthesis by inhibiting mRNA-PTB (Polypyrimidine Tract-Binding Protein) complex formation in hepatocytes (37).

The BCAA/AAA ratio positively correlates with albumin synthesis and secretion and response to BCAA supplementation. If the BCAA/AAA ratio is low, adding BCAA does not significantly affect the increase in albumin content (38). It is worth noting that BCAA supplementation alone is not optimal for collagen synthesis. This claim is supported by Rajendram et al. (2015), who found that combining BCAA with glutamine could optimize wound healing compared to BCAA alone due to insufficient collagen in wounds with a single treatment (39).

This is consistent with Murakami et al. (2013) and Crozier et al. (2005), who showed that supplementation of BCAA with glutamine significantly increased skin tropocollagen synthesis, suggesting a synergistic effect between BCAA and glutamine (40,41). Montoya et al. (1989) also showed that the administration of an infusion containing only 45% BCAA did not significantly accelerate wound healing compared to a conventional parenteral infusion containing 8% BCAA (42). Zhang et al. (2004) presented an amino acid mixture containing high doses of leucine,

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isoleucine, valine, lysine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine that had anabolic effects on proteins synthesis in rabbit skin wounds. They hypothesized that increasing the availability of amino acids would improve the process of protein synthesis. (43). Wound protein anabolism can initiate the wound healing process because new proteins must be synthesized to repair damaged tissue and improve cellular functions such as cell migration and cell differentiation (43). Mixing BCAA with glycine and BCAA with glycine and arginine synergistically significantly increased the fractional synthesis rate of skin tropocollagen protein in UVB-treated rats (44). In addition, Nair and Chong (2020) found that BCAAs can increase the production of growth hormones, which can help in the wound healing process (45). BCAAs are also related to strengthening the immune system, but the exact mechanism is still not well understood (34).

Moss et al. (1970, 1975, and 1984) found that elevated BCAA levels in postoperative patients decreased protein catabolism and increased protein anabolism. This is reflected in the increased production of plasma proteins and wound healing when the following patients are administered a high-nitrogen-calorie diet (Vivonex R containing 3600-4800 kcal and 150-200 g protein equivalent) via a nasoduodenal tube following elective open cholecystectomy. A significant increase in serum BCAA levels was observed within the first 2 hours after dosing and remained high throughout the duration of tube feeding (46–48). BCAAs can act as a precursor to glutamine and alanine synthesis during catabolic states, providing additional nutrition and maintaining nitrogen balance after surgery (49). Research conducted by Choudry et al. (2006) found that administering the parenteral nutrition fluid BFLUID (containing 30% BCAA) resulted in higher tensile strength compared to the group given Physio35 (which does not contain amino acids) ($p<0.05$). There was a significant increase in type 1 collagen mRNA expression ($p<0.05$) compared to the Physio35 group and an increase in type 3 collagen mRNA expression compared to the Physio35 group ($p<0.1$) (49). Delany HM et al. (2011) showed no difference in wound healing between enteral and parenteral administration of a high BCAA diet in patients undergoing major surgery. (50).

BCAAs can also be given in topical dressing formulations together with other amino acids. One study showed that topical dressings containing leucine, glycine, lysine, and sodium hyaluronate improved wound healing in rats. The mechanism is thought to involve increased immunolocalization of TGF-beta in the dressing region. Stimulated TGF-beta can increase fibroblast production and eNOS secretion, and it is designed to increase collagen and reduce inflammation. Leucine is an essential amino acid that promotes protein synthesis (51).

It's worth noting that it takes 6.5g of BCAAs to reach plasma concentrations, which is five times higher than human basal levels. Leucine, in particular, is a primary stimulator for collagen synthesis in wound healing, especially in conditions of protein undernutrition. However, it's important to remember that single therapy with BCAAs alone is not effective for dermal collagen synthesis (39).

The maximum tolerated dose for leucine, isoleucine, and valine is 500 mg/kg/day (52). It is important to note that BCAA supplements should be used with caution in individuals with co-morbidities such as diabetes and psychiatric disorders. Increased BCAA concentrations promote insulin resistance, which can accelerate other diabetic complications. BCAAs can also increase aggression and lower mood by reducing serotonin synthesis (53).

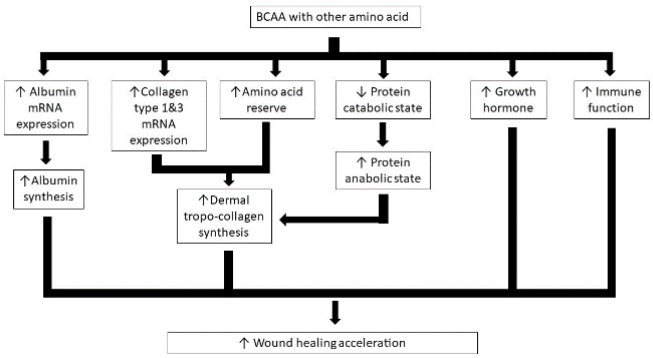

Figure 1. Mechanism of BCAA on Wound Healing Process.

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CONCLUSION

BCAA is an essential amino acid that can help in the wound healing process. However, the availability of other essential amino acids such as glutamine, arginine, glycine, and others is necessary to optimize their effectiveness. BCAAs can be administered orally, parenterally, enterally, or topically as wound dressings.

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