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Revisiting the Role of Micronutrients in the Healing Process of Burn Injury

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ABSTRACT

Burn injuries are an under-appreciated trauma that can affect anyone, anytime and anywhere. The injuries can be caused by friction, cold, heat, radiation, chemical or electric sources, but the majority of burn injuries are caused by heat from hot liquids, solids or fire. Micronutrients are vitamins and minerals needed by the body in very small amounts. Micronutrients (vitamins and minerals) have numerous health benefits including tissue maintenance, bone and teeth formation and health, serving as cofactors and coenzymes to enzyme various enzyme systems, aiding the regulation and coordination of most body functions, and other biochemical and physiological functions in the body. Major burns require a comprehensive approach addressing both burn severity management and nutritional support. Micronutrients, such as vitamin C, zinc, and vitamin D, play indispensable roles in wound healing, immune function, and overall well-being. Challenges in micronutrient interaction, genetic factors, and patient variability underscore the importance of personalized nutrition therapy in burn care. Future research should explore optimal micronutrient dosages, duration of effectiveness, and potential long-term effects, while precision medicine approaches could enhance burn care by addressing inflammation and infection challenges. Burn management should also integrate precision medicine approaches, recognizing role of inflammation to enhance burn care by mitigating the impact of the hypermetabolic state and providing optimal nutrition. The focus on high-carbohydrate diets, protein supplementation, and careful attention to micronutrient replacement aligns with the goal of meeting heightened caloric needs while minimizing overfeeding.

KEYWORDS: micronutrients, burn injury, vitamin C, zinc, vitamin D, omega 3 fatty acid

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INTRODUCTION

Burn injuries, a frequently underestimated trauma, can impact individuals at any time and in any place. These injuries result from various sources such as friction, cold, heat, radiation, chemical, or electric exposure. However, the primary cause of burn injuries stems from the heat generated by hot liquids, solids, or fire. Economically and culturally marginalized countries bear a higher incidence of these injuries. According to WHO data, approximately 180,000 people succumb to burns globally each year.[1]

Determining the cause of a burn injury is crucial, and it is equally important to categorize the injury based on its severity, considering both depth and size. Superficial (first-degree) burns affect only the outermost layer of the skin (epidermis), resulting in redness and limited, short-lived pain. Superficial partial-thickness (second-degree) burns (also known as 2A burns) are painful, weep, and necessitate dressing and wound care, potentially leading to scarring, but they don't require surgery. On the other hand, deep partial-thickness (second-degree) burns (also known as 2B burns) are less painful due to partial destruction of pain receptors, require surgery, and result in scarring. Full-thickness (third-degree) burns extend through the entire dermis, are typically painless due to nerve damage, and demand protection against infection, often necessitating surgical management for larger cases. Fourth-degree burns, involving deeper tissues like muscle or bone, present as blackened and frequently lead to loss of the affected part. While superficial and superficial partial-thickness burns often heal without surgical intervention, more severe burns demand careful management, including the use of topical antimicrobial dressings and, if necessary, surgical procedures.[2]

Once burn injury severity is determined, promptly refer and triage the patient. Managing major burn injuries is resource-intensive and typically occurs in specialized centers, significantly impacting not only the patient life but also that of caregivers and families for an extended period. A recent study revealed that burn injuries influence morbidity and mortality for at least 5–10 years post-injury. Therefore, those engaged in burn care should shift their focus from immediate survival to goals addressing scarring, long-term well-being, mental health, and overall quality of life.[2]

Historical perspective on nutritional support in burn care

In the 18th century, Sir John Hunter observed the catabolic response to injury. The phases of injury, termed 'ebb' and 'flow,' were distinctly documented in the early 1940s by Scottish nutritional scientist David Cuthbertson, who studied mineral excretion in fracture patients. The 'ebb' phase, occurring within 48 hours of burns (also known as the acute or shock phase), is marked by reduced metabolic rate, depressed oxygen consumption, cardiac output, and glucose tolerance. Survivors transition to the 'flow' or chronic response phase, characterized by an elevated hyperdynamic state, increased metabolism, and cardiac output.[3]

The heightened hypermetabolism observed in severe burn injuries triggers significant catabolism, marked by accelerated glycolysis, proteolysis, and lipolysis, resulting in weight loss and the depletion of lean body mass (LBM). This process contributes to generalized fatigue and a compromised immune response. The impact of LBM loss is particularly dire for patients, as research indicates that a 10% reduction correlates with impaired immunity, a 20% reduction leads to decreased wound healing, and a 40% reduction results in death. To mitigate the hypermetabolic response, various therapeutic strategies have been developed, encompassing environmental control, excision of injured and dead tissue to reduce inflammatory stimulation, nutritional support, and pharmacological interventions.[3]

Since the early 1900s, the recognition of heightened caloric needs in burn patients has evolved. Burn patients necessitate a diet rich in both protein and calories, complemented by multivitamins and trace elements. The mode of feeding plays a crucial role; parenteral nutritional support has been demonstrated to be detrimental, increasing both immune deficiency and mortality. Consequently, continuous enteral feeding is recommended. Recent evidence, reviewed to shape recommendations by the European Society for Clinical Nutrition and Metabolism (ESPEN), underscores the importance of early enteral feeding through the nasojejunal or nasoduodenal route for burn patients.[4,5]

Significance of Micronutrients

Micronutrients, comprising vitamins and minerals, play crucial roles in the body at minimal intake levels. They contribute significantly to health by supporting tissue maintenance, fostering bone and teeth health, acting as essential cofactors and coenzymes in diverse enzyme systems, and facilitating the regulation and coordination of various bodily functions. These micronutrients are indispensable for humans and other organisms, required in varying quantities throughout life to sustain optimal physiological functions and overall well-being.[6]

Humans require micronutrients in amounts generally below 100 milligrams per day, in contrast to the gram-per-day requirement for macronutrients. Micronutrient needs encompass vitamins, organic compounds necessary in micrograms or milligrams. In 2019, the WHO added a multiple micronutrient powder containing at least vitamin A, iron, and zinc to its List of Essential Medicines. During the 1990 World Summit for the Children, participating countries identified deficiencies in two microminerals and one micronutrient (iron, iodine, and vitamin A) as prevalent and posing health risks in developing nations.[6]

To gain deeper understanding regarding the role of micronutrients in the healing process of burn injury, we conduct this literature review collecting scientific facts from both national and international literatures from PubMed and Google Scholar databases. We included relevant full paper studies discussing micronutrients with burn wound healing in Indonesian and English language from the last 10 years, including case reports, retrospective studies and systematic reviews.

Importance of micronutrients in physiological processes, including wound healing

The skin, human largest organ by surface area, critically protects internal tissues from mechanical damage, microbial infection, ultraviolet radiation, and extreme temperature. Its vulnerability to injury has a substantial impact on both individual patients and the healthcare economy.[7]

Cutaneous wound healing is a vital physiological process involving the coordinated interaction of various cell strains and their products. The initiation of efforts to repair the damage caused by local aggression occurs early in the inflammatory stage. Ultimately, these efforts lead to both repair, involving the replacement of specialized structures through collagen deposition, and regeneration, marked by the proliferation and subsequent differentiation of cells from pre-existing tissue and/or stem cells. Importantly, these mechanisms are not mutually exclusive; in the aftermath of a skin lesion, regeneration and repair can coexist in the same tissue, contingent upon the cell strains affected by the injury.[7]

Tissue regeneration and repair follow the onset of a lesion, whether caused by trauma or a specific pathological condition. All stimuli that disrupt the physical continuity of functional tissues create a lesion. These stimuli, whether external or internal, may be physical, chemical, electric, or thermal. Additionally, lesions can lead to damage in specific organelles or entire cells.[7]

In tissue repair, growth factors stimulate cell proliferation, facilitating the integration of dynamic changes encompassing soluble mediators, blood cells, extracellular matrix production, and parenchymal cell proliferation. Wound repair

involves distinct stages: an inflammatory reaction, cell proliferation with extracellular matrix synthesis, and a subsequent remodeling period. These stages exhibit temporal overlap rather than strict mutual exclusivity.[7]

In burn patients, nutritional status is coupled to the stage of injury. Nutritional assessment consequently is a dynamic, ongoing process. At the time of admission, factors related to the pre-burn history (including days post-burn, prior burn care and any complicating injuries), pre-injury height and weight, and clinical appearance serve as the basis for initial nutritional assessment. Patients who are malnourished (often those patients whose admission is significantly delayed from the time of injury) should be quickly identified since they are at greatest risk for re-feeding syndrome with the initiation of nutrition support.[8-10]

Micronutrients and Their Role in Burn Healing

Vitamin C

Vitamin C, or L-ascorbic acid, is a water-soluble vitamin naturally found in some foods, added to others, and offered as a dietary supplement. Unlike most animals, humans cannot internally produce vitamin C, making it an essential dietary element. This vitamin is crucial for synthesizing collagen, L-carnitine, and certain neurotransmitters, as well as participating in protein metabolism. Collagen, integral to connective tissue and vital for wound healing, relies on vitamin C. Acting as a physiological antioxidant, vitamin C not only regenerates other antioxidants like alpha-tocopherol (vitamin E) but also limits free radical damage, potentially preventing or delaying diseases with oxidative stress involvement, such as certain cancers and cardiovascular diseases. Beyond its biosynthetic and antioxidant roles, vitamin C enhances immune function and facilitates nonheme iron absorption from plant-based foods. Inadequate vitamin C intake leads to scurvy, manifesting as fatigue, widespread connective tissue weakness, and fragile capillaries. Ongoing research explores the potential of vitamin C in preventing various diseases through its antioxidant capabilities.[11]

Oral vitamin C tightly regulates tissue and plasma concentrations in the body. Human bodies absorb about 70%–90% of vitamin C with moderate intakes of 30–180 milligrams per day. However, doses exceeding 1 grams per day result in absorption dropping to less than 50%, leading to the excretion of unmetabolized ascorbic acid in urine. Pharmacokinetic studies reveal that a daily oral dose of 1.25 grams ascorbic acid yields mean peak plasma vitamin C concentrations of 135 micromols/litre, approximately twice those achieved by consuming 200–300 milligrams per day ascorbic acid from vitamin C-rich foods. Pharmacokinetic modeling predicts that even with doses as high as 3 grams ascorbic acid every 4 hours, peak plasma concentrations would only reach 220 micromol/litre. Total content of vitamin C in human body varies from 300 milligrams (near scurvy) to about 2 grams. Cells and tissues maintain high vitamin C levels (millimolar concentrations), with the highest concentrations observed in leukocytes, eyes, adrenal glands, pituitary gland, and the brain. Conversely, extracellular fluids, including plasma, red blood cells, and saliva, contain relatively low levels of vitamin C (micromolar concentrations).[12]

Evidence on impact of vitamin C on collagen synthesis and immune function

Vitamin C plays a crucial role in connective tissue healing by serving as a cofactor for prolyl hydroxylase and lysyl hydroxylase enzymes. These enzymes actively catalyze the hydroxylation of proline and lysine residues in procollagen, facilitating the proper folding of the stable collagen triple-helix conformation. Beyond its involvement in collagen synthesis, vitamin C functions as a potent antioxidant, actively neutralizing harmful reactive oxygen species (ROS) that contribute to cell apoptosis during the inflammatory phase. Studies in cell culture have additionally demonstrated that vitamin C induces the mobilization of tendon-derived stem cells, promotes the growth and differentiation of osteoblasts, and stimulates fibroblasts.[13] Vitamin C, in addition to its antioxidant properties, plays a crucial role in regulating collagen synthesis. It is well-documented that vitamin C actively participates in the hydroxylation process of collagen molecules. This hydroxylation is essential for ensuring the extracellular stability of collagen and providing support to the epidermis. Moreover, vitamin C has demonstrated its ability to stabilize collagen mRNA, leading to an enhanced synthesis of collagen proteins to facilitate skin repair. Simultaneously, there is a concomitant reduction in elastin production, a protein often overproduced in response to photodamage. Additionally, vitamin C promotes the proliferation of fibroblasts, a capacity that diminishes with age. Furthermore, vitamin C stimulates DNA repair in cultured fibroblasts.[14]

Clinical trials assessing the supplementation of vitamin C in burn patients

Vitamin C, extensively researched in postburn injuries for its diverse role in reducing fluid requirements and wound edema, exhibits mechanisms such as vitamin E regeneration, ROS scavenging, lipid peroxidation reduction, and collagen denaturation inhibition. The consideration of intravenous vitamin C as an adjuvant therapy for burn patients in the acute phase has gained significance. Soltany and colleagues (2022) emphasized a recommended daily intake of 80–100 mg, with well-tolerated oral doses up to 10 grams due to its water solubility and low metabolism. The precise vitamin C dose for burn resuscitation remains undetermined. Preclinical animal studies suggest 14.2 milligrams per kilogram of body weight per hour, but concerns arise from its hydrophilicity and rapid renal excretion. High-dose vitamin C in burns, documented in 6 cases, led to calcium oxalate nephropathy and clinical acute kidney injury. Monitoring urine output, haematocrit, haemodynamic, serum osmolality, and urine osmolality is crucial to prevent complications such as osmotic diuresis exacerbating acute kidney injury.[15]

Malkoc and colleagues (2022) highlighted crucial role of ascorbic acid in enhancing outcomes in burn care. Although the benefits of commencing ascorbic acid administration during burn resuscitation are acknowledged, an optimal effective dosage remains undefined. In their clinical retrospective study comparing low and high-dose ascorbic acid administration, a dosage of 15000 milligrams over the initial 72 hours exhibited a potential protective influence on time to first infection and mortality rate.[16] Previously, Tanuwijaya and colleagues (2020) recommended vitamin C as adjuvant therapy in the prevention of burn sepsis as vitamin C as a reactive oxygen species (ROS) scavenger reduces the fluid requirement in burn resuscitation.[16] The studies suggest that, despite a higher total body surface area (TBSA) of burn wounds and increased fluid administration in the initial days, a high intravenous dose of vitamin C positively impact burn resuscitation and mortality.[16,17]

Zinc

Zinc, an essential micronutrient, is found in the human body at levels below 50 milligrams per kilogram of body weight. It plays a crucial role in human health and disease by actively participating in growth, development, bone metabolism, the central nervous system, immune function, and wound healing. Acting as a vital cofactor for over 10% of proteins encoded by the human genome (approximately 3000 proteins or enzymes), zinc-dependent proteins serve essential functions within cells, including transcriptional regulation, DNA repair, apoptosis, metabolic processing, extracellular matrix (ECM) regulation, and antioxidant defence. Zinc deficiency contributes to increased oxidative stress, a well-established factor in tissue injury, with redox regulation playing a key role in wound repair. Reactive oxygen species (ROS) and reactive nitrogen free radical species (RNS), such as superoxide radicals, are by-products of electron leakage during mitochondrial electron transfer. These radicals constitute various forms of oxidative stress, causing damage to biomolecules like DNA, proteins, and lipids, thereby compromising their bioactivity.[18]

Studies exploring the relationship between zinc level status and burn outcomes

Thermal burn patients experience zinc deficiency due to exudative losses, increased urinary excretion, and reduced carrier proteins, resulting in compromised immunity, impaired wound healing, and glucose control. Putri and colleagues (2021) highlighted the significance of zinc as a trace element in wound healing, particularly during the proliferative phase. This phase involves the activation of T regulatory cells, increased fibroblast activity, and deposition of collagen and extracellular matrix. Zinc contributes to the elevation of T regulatory cell numbers, regulating inflammation, promoting re-epithelialization, and enhancing wound contraction. Additionally, zinc influences fibroblast activity post-burn, with fibroblasts entering the wound site after two or three days to accumulate and facilitate collagen and extracellular matrix deposition. This deposition acts as a scaffold for wound repair, supporting the development of new epithelium, keratinocytes, and microvasculature. The extracellular matrix deposition engages cell signalling via the TGF-β signalling - Smad protein pathway, where zinc, as a cofactor for Smad signalling, plays a crucial role in granulation tissue formation. During new epithelium formation, there is proliferation and migration of keratinocytes, fibroblasts, epithelial cells, and endothelial cells, alongside activation and differentiation of multiple epidermal stem cells. Zinc has been demonstrated to enhance keratinocyte migration and contribute to the re-epithelialization of the epidermis.[19]

Optimal dosage and duration of zinc supplementation in burn patients

The human body stores 2–4 grams of zinc in the prostate, eyes, brain, muscles, bones, kidneys, and liver. Albumin (60%) and transferrin (10%) actively bind and transport zinc in blood plasma. For adult burn patients, a recommended intravenous supplementation dose is 37.5 milligrams of zinc per day. The duration of supplementation depends on the severity of the thermal injury; for more extensive burns, the supplementation period should be extended to 14 days.[20]

Vitamin D

The immune system actively defends against foreign invaders, fostering protective immunity while maintaining self-tolerance. Recent insights highlight the impact of vitamin D deficiency on immunity, indicating an elevated susceptibility to infection and autoimmune tendencies in genetically vulnerable individuals. Vitamin D primarily regulates calcium balance and supports bone health by enhancing calcium absorption in the small intestine, stimulating osteoclast differentiation, and promoting calcium reabsorption in bones. It also facilitates mineralization of the collagen matrix in bones. Humans acquire vitamin D through diet or skin synthesis. Both vitamin D2 (ergocalciferol) and D3 (cholecalciferol) can fortify foods, exhibiting similar biological activities. These forms, sensitive to oxygen and moisture, interact with minerals. To maintain stability, commercial applications often use a dry, stabilized vitamin D form with antioxidants like tocopherol. Vitamin D fortification is common in milk, dairy products, and margarines. In regions with limited sunlight exposure, especially during winter or among individuals covering up for cultural reasons, vitamin D deficiency risk increases. Fortifying milk and margarine with vitamin D (aiming for 200 IU per day) proves effective in addressing this challenge.[21]

Review of studies investigating the role of vitamin D in burn injury recovery

Insufficient literature exists on vitamin D status and its impact on outcomes in certain sub-populations, including thermal injury patients. Despite limited studies on vitamin D levels in burn patients, clinicians has long observed that vitamin D levels decrease after thermal injury, potentially due to the injury itself or responses to clinical interventions like fluid

resuscitation and pressure garments. Persistent low serum vitamin D levels, lasting at least a year, have been noted in major burn patients. Long-term assessments indicate lower quadriceps muscle strength at 12 months, although not statistically significant. Wound scarring is another long-term consequence of thermal injury.

Gottschlich et al. administered ergocalciferol to children, noting lower serum calcidiol and calcitriol in supplemented individuals post-burn. A separate study by Kelin et al. using 400 IU daily in pediatric burn patients revealed oral supplements inadequately corrected vitamin D deficiency. Both studies, however, suffered from a shortcoming in term of using ergocalciferol instead of a more effective cholecalciferol to raise serum levels of vitamin D, especially in burn patients.. Another study by Gottschlich compared vitamin D2 and D3 efficacy in critically ill burn patients, recommending continued treatment with vitamin D3 beyond the acute phase.[22]

Limited literature exists on vitamin D levels in adult burn patients and their outcomes, though decreased calcidiol in burn patients is documented. The pathophysiology involves decreased skin surface area post-burn, leading to reduced vitamin D synthesis and delayed wound healing. Burn patients experience reduced effective surface area for vitamin D production, impaired biosynthetic functions, and decreased 7-dehydrocholesterol levels, hindering conversion to cholecalciferol. Adams and Hewison reviewed vitamin D metabolism in burn patients, highlighting the need for larger doses in the restoration phase, although cautioning against potential adverse effects. Further investigation is necessary for understanding vitamin D deficiency prevalence in adult burn patients, its correlation with post-burn sequelae, and potential outcome measures for symptom relief in acute care. Additional studies are required to determine appropriate supplementation forms, dosing regimens, and potential long-term supplementation needs.[22]

Consideration of sunlight exposure and endogenous synthesis in burn patients

Understanding the unique physiology of specific pathological conditions poses a significant challenge in determining nutrient requirements. Taking childhood burns as an example, we explore the impact of inflammatory and stress responses on bone dynamics. The burn triggers a transient surge in bone resorption, leading to osteoblast apoptosis and adynamic bone. Consequently, the bone fails to absorb and retain the excess calcium released during heightened resorption. Additionally, cytokine-mediated upregulation of the parathyroid gland calcium-sensing receptor induces hypocalcemic hypoparathyroidism, causing urinary calcium wasting. Adding to the complexity, burned patients exhibit reduced conversion of 7 dehydrocholesterol to pre-vitamin D3 in both scarred and adjacent skin, resulting in chronically low levels of 25-hydroxyvitamin D. In summary, burn injuries contribute to calcium wasting, impaired bone calcium uptake, and insufficient to deficient vitamin D levels. Addressing these aspects is crucial for determining appropriate vitamin D and calcium supplementation in severe burn cases.[23]

Vitamin D, a sun-derived substance present on Earth for over 500 million years, forms when 7-dehydrocholesterol in the skin absorbs UV B radiation during sunlight exposure, transforming into previtamin D3. This compound subsequently isomerizes into vitamin D3. Both previtamin D3 and vitamin D3 undergo conversion, absorbing UV B radiation and generating various photoproducts, some with distinct biological properties. The synthesis of sun-induced vitamin D is significantly influenced by factors such as season, time of day, latitude, altitude, air pollution, skin pigmentation, sunscreen use, passage through layers like glass or plastic, and aging. Sequentially metabolized in the liver and kidneys, vitamin D transforms into 25-hydroxyvitamin D, a major circulating form, and 1,25-dihydroxyvitamin D, the biologically active form. The latter plays a crucial role in regulating calcium and phosphate metabolism for sustaining metabolic functions and skeletal health. Numerous cells and organs throughout the body possess vitamin D receptors, enabling them to produce 1,25-dihydroxyvitamin D.[22]

Burn is a severe injury marked with significant pathophysiological immune-inflammatory response. Thermal injury induces a unique “genomic storm” altering 80% of the leukocyte transcriptome leading to prolonged simultaneous and rapid stimulation of innate (both pro- and anti-inflammatory genes) and suppression of adaptive immune responses. Clinical studies have recently characterized the immune response following burn injury demonstrating prolonged neutrophil dysfunction and release of immature granulocytes lasting up to 28 days, reduced numbers and impaired expression of CD14+/HLA-DR+ monocytes persisting up to 30 days, and downregulation of NKG2D (a natural cytotoxicity receptor in natural killer cells) ligands resulting in immunosuppression. The presence of concurrent upregulation of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-10, and other cytokines following injury indicates an overcompensating response, which may last for up to 3 years post-burn.[23]

Omega-3 Fatty Acids

Nutritional support significantly improves wound healing, reduces hospitalization, and lowers mortality rates in burn patients. Using fish oil as a primary source of omega-3 fatty acids in nutritional support can mitigate the inflammatory response and boost immune function. Nonetheless, the impact of fish oil on enhancing clinical outcomes in burn patients remains uncertain.[24]

Insufficient nutrient intake during infections lengthens hospital stays, heightening sepsis and organ failure risks, ultimately increasing mortality. Long-chain omega-3 fatty acids play crucial roles with diverse health benefits, such as anti-inflammatory, anti-arrhythmic, immunomodulating, and cardiovascular effects. Enteral nutrition, incorporating

omega-3 supplements, holds potential in reducing mortality and morbidity for burn patients by suppressing inflammation and modulating immune functions post-burn. Studies reveal that supplementing fish oil, abundant in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in daily intake can lower energy expenditure, shorten intensive care stays, ventilation duration, and mortality without adverse effects in acute respiratory distress syndrome patients. International guidelines advocate early enteral feeding of low-fat diets with or without omega-3 post-severe burns to enhance infection control and postpone muscle degradation. Furthermore, parenteral immunonutrition with omega-3, in conjunction with antioxidants and amino acids, demonstrates the potential to alleviate severe inflammatory responses in burn patients.[24]

Clinical trials evaluating the supplementation of omega-3 fatty acids in burn care

The European Society for Clinical Nutrition and Metabolism (formerly the European Society for Parenteral and Enteral Nutrition, ESPEN) guidelines emphasize the positive impact of low-fat (15% of energy requirement) and adequate-protein nutritional support in burn patients, reducing hospital stay length and infection risk. However, the comparative advantage of omega-3 fatty acids over other fats remains uncertain. Systematic reviews and meta-analyses found no evidence supporting superior benefits of omega-3 fatty acid-containing nutritional support over alternative diets in terms of hospital stay length (LOS), mortality, ventilation days, gastrointestinal complications, or infections in burn patients.[24]

In the context of burn injury, elevated immune response and hypermetabolism would aggravate the burn severity and mortality risk. Omega-3 fatty acids prevent the overreactions of arachidonic acid cascade into pro-inflammatory eicosanoids (prostaglandins, thromboxanes, leukotrienes) in human bodies, resulting in the less inflammatory pathways or the resolution of inflammation.[24]

The study by Garrel and colleagues suggested that omega-3 or fish oil containing diets did not have any additional benefit in reducing length of stay due to the similar outcomes between fish oil and low-fat diets. Contrarily, the comparative outcomes in different populations receiving omega-3-containing nutritional support were noted. In patients with gastrointestinal malignancies, postoperative enteral nutrition with omega-3 fatty acids and supplemental arginine improved clinical outcomes by significantly reducing hospital length of stay. The combined immunonutrition may provide advantages in specific conditions of traumatic or critically ill patients, but they were not obviously noticed in burn patients with regard to mortality, length of stay, and infectious complications.[24]

Optimal dosage and duration for therapeutic effects

Omega-3 fatty acids (OM3FAs) are unsaturated fatty acids with at least one double bond between the third and fourth omega end carbon. The three most clinically relevant omega-3 polyunsaturated fatty acids (PUFAs) are α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). These fatty acids are present in oils from plant sources, fish, fish products, seeds, nuts, green leafy vegetables, and beans. The FDA currently approves two new prescription omega-3 fatty acid products (OM3FAs), namely icosapent ethyl which exclusively contains ethyl esters of EPA and omega-3-acid ethyl esters which contain both EPA and DHA. Two previously approved –but now discontinued—prescriptions are omega-3-carboxylic acids and omega-3-acid ethyl esters A; both contain EPA and DHA.[25]

For adults (older than 18 years of age) with hypertriglyceridemia (≥ 500 milligrams/dL), FDA-approved uses of omega-3 fatty acids (OM3FAs) as an adjunct to diet and exercise are as follows: Icosapent ethyl is administered at a daily dose of 4 grams, taken as two 2-gram capsules twice a day with meals. Omega-3-acid ethyl esters are administered at a daily dose of 4 grams, taken as 4 capsules once a day with meals or two capsules twice a day with meals. Omega-3-carboxylic acids are administered at a daily dose of 2 grams, taken as 2 capsules once per day or 4 grams as 4 capsules once a day. Administration during clinical trials was irrespective of meals. Omega-3-acid ethyl esters A are administered at a daily dose of 4 grams, taken as 4 capsules once a day with meals or two capsules twice a day with meals.[25]

It is recommended to take all OM3FAs supplements whole, without crushing, chewing, or dissolving in the mouth. If a dose is missed, patients should take it as soon as remembered and avoid doubling the dose if the next capsule is due. Over-the-counter dietary supplements in various chemical forms are available, but as they lack FDA approval, they are not obligated to demonstrate safety and efficacy before marketing the product.[25]

Challenges and Controversies

Challenges include how micronutrients interact to each other and to toher substances. Vitamin C, vitamin D, and zinc collaboratively contribute to wound healing. Vitamin C serves as a cofactor for enzymes in collagen, carnitine, and neurotransmitter biosynthesis; acts as a water-soluble antioxidant; and boosts the gastrointestinal absorption of non-heme iron. Vitamin D, a fat-soluble vitamin, regulates calcium and phosphorous homeostasis, crucial for bone formation and resorption. Zinc, vital for numerous transcription factors and enzymes, plays a central role in cellular differentiation and proliferation. Together, these nutrients enhance and modulate the immune system, supporting innate and adaptive immunity, including epithelial barriers, cellular defense, and antibody production. Deficiencies in vitamin C, vitamin D, and zinc significantly impair immune responses, increasing the risk of infections during wound healing.[26]

Iron supplementation can hinder zinc absorption, but no such impact occurs when both are present in a meal as fortificants. The rising environmental levels of cadmium also impede zinc

absorption. Adequate absorption of the fat-soluble vitamin D necessitates a specific amount of fat in the diet.[27]

High-dose vitamin C (more than 66 milligrams per kilogram of body weight per hour) may decrease fluid requirement, improve edema, and improve wound healing time when given to adult patients with first- and second-degree burns involving 10 to 40% total body surface area (TBSA) on the first day of admission. One study stated a high ascorbic acid dose of 15,000 milligrams over the first 72 hour had a potential protective effect on time to first infection and mortality rate, showing that even with a greater TBSA of burn wounds and larger amounts of intravenous replacement fluid given in the first days, a high dose of intravenous ascorbic acid may have a positive impact in burn resuscitation and mortality.[16]

The suggested doses of additional intravenous supplementation zinc in adult burn patients is 37.5 milligrams per day. The actual amount of absorbed zinc not only depends on the zinc content of the consumed diet, but is highly affected by its intestinal zinc bioaccessibility and bioavailability. Bioavailability of zinc may be influenced by protein consumption due to zinc's protein requirement in order to be transported to different areas in the body. The patient in this case has consumed an adequate amount of protein as indicated by ESPEN nutrition guideline for patients with burn injury (1,5 - 2 grams per kilogram of body weight).[20]

Vitamin D actively maintains calcium balance and supports bone health by boosting calcium absorption in the small intestine and fostering osteoclast differentiation and bone calcium reabsorption. Kelin and colleagues administered 400 IU of daily vitamin D to paediatric patients with extensive burns, but such treatment provided inadequate correction of the deficiency and consequently proved oral supplementation is ineffective in restoring vitamin D serum levels in burn patients. However, both studies were hindered by the limitation of the chosen supplement.

Individual variability of genetic factors influencing micronutrient metabolism

The interaction between nutrition, metabolism, and gene expression is mandatory for maintenance of body homeostasis. Many reports suggested nutrition related or dependent disorders involving multiple genes not a single gene. Genetic variation is the major basis for person-to-person divergence in response to diet. Understanding how genetic variation influences gene expression and recognizing genetic variants as risk factors for human nutrition dependent or related disorders is the focus of nutrigenetics.[27] Intrinsic factors such as genetic variations control the efficacy of metabolic pathways by affecting the function and specific activities of membrane transporters, receptors, signalling proteins, enzymes, carrier proteins, transcription factors, and other proteins involved in the transport sensing and processing of specific nutrients.[10]

Variability in patient response to micronutrient supplementation

Extrinsic factors like food, xenobiotics, and the environment, along with intrinsic factors such as sex, age, and gene variations, independently and collaboratively impact nutrient metabolism. Sex and aging play pivotal roles in shaping the biological context, serving as significant modifiers of metabolic efficiency. Males and females exhibit distinct features, including disparate metabolic profiles, gene expression programs, and susceptibility to diseases. Aging, marked by the deterioration of cellular and genetic components due to accumulated chemical damage throughout life stages, leads to a decline in metabolic efficiency. At the cellular level, aging is linked to gradual changes in processes aimed at maintaining homeostasis. However, these adaptive alterations in cellular metabolism may contribute to a diminished metabolic efficiency at the organismal level. Remodeling of the epigenome throughout life stages may also influence disease susceptibility in elderly individuals.[10]

External factors significantly influence nutrient metabolism and health outcomes. Physical cues, such as photoperiod and temperature, play a crucial role. The day-night cycles' alternating light/dark periods are particularly essential, setting endogenous circadian rhythms closely tied to metabolic regulation. Detrimental environments, triggering stress hormone release, can hinder human ability to sense and respond to metabolic challenges. Moreover, extrinsic factors induce epigenomic alterations with enduring effects on nutrient and energy metabolism. These changes contribute to the development of metabolic disorders in organs like the heart (e.g., coronary heart disease) and the brain (e.g., Alzheimer's disease).[10]

Future Directions

Micronutrients are essential in nutrition support of burn patients because of their roles in immune function and increased needs due to wound healing. Some lesser-known but emerging micronutrients deserve further investigation to unveil their potential roles. Iron acts as a cofactor for oxygen-carrying proteins, and boosts cell-mediated immunity. Copper is crucial for wound healing and collagen synthesis, and its deficiency has been implicated in arrhythmias, decreased immunity, and worse outcomes after burn injury.

Future researches should investigate the optimal micronutrient dosage for burn patients, enabling precise application in clinical practice. Additionally, it is crucial to compare the duration of micronutrient effectiveness in burn patients and assess any potential long-term involvement or side effects in patients undergoing extended burn treatment.

Future directions in burn management involve personalized nutrition therapy focusing on micronutrient support. The primary objective for nutritional intervention in burn patients is meeting heightened caloric needs induced by the hypermetabolic state, while avoiding overfeeding. Burn patients benefit from high-carbohydrate diets, promoting wound healing and minimizing muscle protein degradation

more effectively than high-fat diets. Fat is essential to prevent essential fatty acid deficiency but is recommended in limited quantities. Post-burn, lipolysis is suppressed, decreasing lipid utilization for energy; however, increased beta-oxidation of fat serves as fuel during the hypermetabolic state.[29]

Protein supplementation is needed to meet ongoing demands and supply substrate for wound healing, immune function, and to minimize the loss of lean body mass. Protein is used as an energy source when calories are limited; however, the opposite is not true. Currently, protein requirements are estimated as 1.5–2.0 grams per kilogram of body weight per day for burned adults and 2.5–4.0 grams per kilogram of body weight per day for burned children. The metabolism of numerous "micronutrients" (vitamins and trace elements) is beneficial after burn as they are important in immunity and wound healing. Severe burn leads to an intense oxidative stress, which combined with the substantial inflammatory response, adds to the depletion of the endogenous antioxidant defenses, which are highly dependent on micronutrients. Replacement of these micronutrients has been shown to improve the morbidity of severely burned patients.[29]

Precision medicine, also known as "personalized medicine" is an innovative approach to tailoring disease treatment that considers differences in genes, environments, and lifestyles. Burn management should integrate precision medicine approaches, recognizing the role of inflammation in successful wound healing. Treatment of inflammation in large burns is vital but difficult. Traditional anti-inflammatory treatments that focus on the inhibition of prostaglandin synthesis, such as non-steroidal anti-inflammatory drugs or glucocorticoids, impair wound healing. Early excision and grafting has become the gold standard for treatment of full and deep partial thickness burns, in part because early excision helps reduce the risk of infection and scarring. The timing of debridement coincides with the inflammatory phase of healing, as the burn eschar removed during excision is an inflammatory nidus and a rich pabulum for bacterial proliferation. The skin functions as a barrier to the external environment to maintain fluid homeostasis and body temperature, while providing sensory information along with metabolic and immunological support. Damage to this barrier disrupts the innate immune system and increases susceptibility to bacterial infection.[30]

Clinicians use antibiotics regularly to treat underlying infections, in order to reduce morbidity and prevent mortality. Topical antimicrobial therapy is often applied to prevent or treat infections, or used as an adjunct (in addition) to surgical treatment or systemic (whole body treatment) antibiotics. However, antibiotics should only be administered properly once an infection has been diagnosed and ideally be matched to the species of microbes causing the infection, and not encourage drug resistance. Accordingly, reducing the impact of a hypermetabolic state and providing adequate nutrition are key factors that affect burn wound healing and recovery.[30]

CONCLUSION

Burn injuries pose a significant global health challenge, particularly in economically disadvantaged regions, with substantial morbidity and mortality. Major burns require resource-intensive care, impacting immediate survival and long-term outcomes. A comprehensive approach addressing both burn severity management and nutritional support is crucial. Micronutrients, such as vitamin C, zinc, and vitamin D, play indispensable roles in wound healing, immune function, and overall well-being. Challenges in micronutrient interaction, genetic factors, and patient variability highlight the importance of personalized nutrition therapy in burn care. Future research should explore optimal micronutrient dosages, duration of effectiveness, and potential long-term effects.

Moving forward, burn management should integrate precision medicine approaches, recognizing the role of inflammation process in successful wound healing. Early excision and grafting, avoiding traditional anti-inflammatory treatments, are crucial. Antibiotics play a key role in preventing infections, matching treatments to the specific microbial species. Precision medicine, tailored to individual needs, can enhance burn care by mitigating the impact of the hypermetabolic state and providing optimal nutrition. The focus on high-carbohydrate diets, protein supplementation, and careful attention to micronutrient replacement aligns with the goal of meeting heightened caloric needs while minimizing overfeeding. The integration of these strategies offers a promising avenue for improving both short-term and long-term outcomes in burn care.

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