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BURNS

REVIEW ARTICLE

ANTIOXIDANTS REDUCE TISSUE NECROSIS IN THE ZONE OF STASIS: REVIEW OF BURN WOUND CONVERSION

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ABSTRACT

Summary: Severe burns are devastating condition identified by loss of hemodynamic stability and intravascular volume. Adequate fluid replacement, nutritional support, and immediate wound grafting can reduce the risk of infection and mortality. Oxidative stress was shown to have significant role in the burn wound conversion, which happens when the zone of stasis can't be salvaged and progresses to necrosis. Decreasing the level of oxidative stress early may be fundamental in reducing burn injury progression into deeper tissue. Several animal studies have demonstrated the advance of antioxidant supplementation for burns outcomes. Approach to this salvageable burn tissue is a breakthrough for new directions in burn management. Antioxidant supplementations was proven to prevent burn conversion on the ischemic zone. Administering antioxidant post-burn is linked with less progression of burn depth and inflammatory cytokine release, which alleviates burn-related morbidity and mortality and improves patient's quality of life. To date, no clinical trials have been done to reproduce similar outcomes of this ROS-scavenging therapy as successfully observed in murine models. Antioxidant supplementation is a promising treatment avenue to halt burn wound conversion following severe burns.
Keywords: *Burn wound, wound conversion, burn management, antioxidant*

Ringkasan: Kasus luka bakar berat ditandai dengan hilangnya stabilitas hemodinamik dan volume intravaskular. Pemberian resusitasi yang memadai, asupan nutrisi, dan *grafting* luka yang tepat dapat mengurangi risiko infeksi dan angka kematian. Stres oksidatif terbukti memegang peranan penting dalam mempercepat konversi luka bakar, yang terjadi ketika zona stasis tidak dapat diselamatkan dan berkembang menjadi area nekrosis. Mengurangi level stres oksidatif penting terbukti mencegah perluasan luka bakar ke jaringan yang lebih dalam. Beberapa penelitian pada hewan coba menunjukkan efek positif suplementasi antioksidan pada luaran pasien dengan luka bakar. Terapi yang tertuju pada jaringan luka bakar pada zona statis merupakan terobosan dalam manajemen luka bakar. Suplemen antioksidan terbukti mencegah konversi luka bakar di zona iskemik. Pemberian antioksidan pasca-luka bakar mencegah progresi kedalaman luka bakar dan supresi pelepasan sitokin inflamasi, yang dapat mengurangi tingkat morbiditas dan mortalitas pasca-luka bakar dan meningkatkan kualitas hidup pasien. Sampai saat ini, belum ada uji klinis yang berhasil membuktikan efek suplementasi antioksidan pada konversi luka bakar seperti yang telah diamati pada uji hewan coba. Suplementasi antioksidan merupakan pilihan terapi ajuvan yang menjanjikan untuk supresi konversi luka bakar pada kasus luka bakar berat.
Kata kunci: *Luka bakar, konversi luka, managemen luka bakar, antioksidan*

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INTRODUCTION

Burns are major health problems causing fatal complications such as infection and even death. Severe burn cases are devastating conditions identified by loss of hemodynamic stability and intravascular volume requiring immediate fluid resuscitation followed by infection control, nutritional support and full wound coverage and grafting.[1] The extent of burn size and depth is positively correlated with length of hospital stay, sepsis, mortality, and the occurrence of burn wound conversion.[2]

Progression of burn wound depth is a poorly understood process when the partial-thickness wounds undergo necrosis and advance into deep full-thickness burns.[3] The eventual depth of the burn wound necrosis following burn injury is not readily apparent. This progressive microvascular deterioration is responsible for increased morbidity and mortality and greatly affect treatment outcome in burn patients.[4] Over the last decade, a lot of studies have researched about preventing burn wound deepening by reevaluating the effects of fluid resuscitation, inflammation and infection control, nutritional requirement, surgical and wound dressing methods, as well as some novel therapeutic approach including the effects of antioxidants supplementation on burn wound conversion.[5] This article aims to deliver an up-to-date summary of the advances in managing burn wound conversion and investigate the promising antioxidant supplementation as a new treatment modality for burn management in the near future.

EVOLUTION OF BURN INJURY

Burn is a complex and dynamic process resulting in a myriad of cellular and metabolic alterations, which alters whole-body responses long after the burn itself.[6] It is categorized into three main groups based on the causes of injury: chemical burns caused by strong acids or alkali; thermal burns caused by fire, hot water, or hot oil; and electrical burns caused by exposure to high voltage current or lightning. Extensive research in burn field has made the intricate and complex cellular pathophysiology of burn becomes clearer.

The classic concept of burn proposed by Jackson burn model categorized burns into three zones of injury: coagulation zone, static zone, and hyperemia zone.[7] The coagulation zone is the core and the other two zones encircle this necrotic part of burn injury. The zone of stasis is a transitional area of active inflammatory process with reduced vascularization and oxygenation. The outermost area is the hyperemic zone, where the vascularization is not impaired. The stasis zone is the most dynamic and highly dependent on early resuscitation because this area progresses to necrosis within 48 hours post-thermal injury if left inadequately treated. This may result in a deeper and wider area of injury within the first 3 days, named burn wound conversion, which may put the patients in greater danger.[7] The zone of stasis is divided into (a) the upper subpart with necrotic endothelial cells and viable adnexal and interstitial cells, which eventually progresses to full necrosis due to ischemia, and (b) the lower zones with initially viable endothelial cells that may progress to necrosis. Hirth et al. observed that these initially viable cells 1-hour post-burn was predictive of tissue necrosis and apoptosis at 24 hours, contributing to dermal ischemia that rapidly converts the partial-thickness burns into full-thickness wounds. Instead of the heat, released soluble factors (inflammatory cells and cytokines) are responsible for immediate necrosis and apoptosis, serving as the leading factor for wound progression.[8]

Burns cause extensive tissue destruction and initiate massive inflammatory reactions leading to local and distant multiorgan alterations. Systemic response following thermal injury is classified into early hypometabolic 'ebb phase' happening within the first 48 hours and hypermetabolic 'flow' phase, which starts after 48 hours.[9] Reduced oxygenation due to inhalation injury as well as decreased cardiac output and peripheral blood flow are the characteristics of the ebb phase.[9] The complex interplay of direct heat on microcirculation and the chemical mediators activated following burns are responsible for the systemic inflammatory cascades, endothelial dysfunction, and excessive capillary leakage. Total body surface area (TBSA) exceeding 20% increases systemic vascular permeability, resulting in loss of intravascular fluid to interstitial space, creating generalized edema and impaired tissue perfusion.[1] Greater burn depth is associated with higher level of circulating cytokines, which may delay wound healing, re-epithelization, and promote systemic infection.[6] Intense loss of plasma may lead to burn shock, thus early repletion of intravascular volume remains the mainstay of burn management within the first 24 hours to

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immediately preserve tissue vascularization and minimize the detrimental effects of inflammatory responses. At the same time, the release of catecholamines, antidiuretic hormone, hemoconcentration may increase pulmonary and systemic vascular resistance.[4]

The hypermetabolic-hyperdynamic 'flow phase' occurs 48-72 hours post-burn. It is characterized by increased oxygen consumption, increased carbon dioxide production, and decreased vascular resistance. The body tries to compensate by increasing cardiac output, enhances blood flow to distant organs, and reabsorbing the edema fluid; leaving the body in a state of hypervolemia, which may cause pulmonary edema and respiratory distress. Release of catabolic hormones and insulin resistance secondary to thermal insults increases protein turnover, gluconeogenesis, and production of urea to compensate massive catabolic processes, which leads to protein denaturation and muscle wasting contributing to burn-induced tissue injury. These metabolic alterations following severe burns may persist up to 2 years and might interfere with wound recovery. Harris-Benedict equation predicted metabolic rates of 110-120% resting energy expenditure up to 2 years post burn.[10]

HYPERMETABOLISM INCREASES BODY STRESS RESPONSE

Burn wounds are characterized by inadequate tissue perfusion, leading to a state of ischemia and tissue hypoxia. The hypermetabolic state induces major stress response and is associated with myriad biochemical alterations at molecular levels. As the body tries to respond to excessive stress, there are 10- to 20-fold increase in plasma catecholamines level as well as glucocorticoids and adrenocorticotropic hormone (ACTH).[3, 4] These catabolic hormones cause inhibition of glycogenesis and rapid-onset insulin resistance, which establish a state of elevated proteolysis, gluconeogenesis, energy consumption, and increased lipid oxidation causing high levels of circulating plasma free fatty acid (FFA).[4] Moreover, thermal burns remarkably decreases total antioxidant at cellular and systemic level early post-burn, and produces free radicals that overwhelm the scavenging capacity of the natural oxidative blocking mechanism.[11]

Free radicals and lipid peroxidation are responsible for systemic inflammatory response syndrome (SIRS) and organ damage in burn injury.[11] Nuclear factor kappa-B (NF-kB) is immediately activated following severe burns, which then initiates a cascade of pro-inflammatory mediators by macrophages altogether with sequestered leukocytes.[12] Prolonged hypermetabolism in early thermal injury also increases the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-6, prostaglandin E2, and induces formation of reactive oxygen species (ROS), such as superoxide anion, hydroxyl peroxide, and reactive nitrogen species (RNS), such as nitric oxide and peroxynitrite.[7] The increased inflammatory mediators in the first few hours of burn injury, especially IL-6, is proportionate to the size of burn area, showing that severe burns is correlated with more pronounced systemic pro-inflammatory activities.[12] Furthermore, pro-apoptotic factors, such as Bax, Bcl-Xl, and caspase-3 are upregulated, causing significant systemic apoptosis.

Excessive ROS production following burn injury is harmful to lipids, proteins, and nucleic acids, which overwhelm endogenous cellular metabolism and the balance between the production of free radicals and detoxifications.[11] Overproduction of ROS and impaired antioxidant mechanisms are closely linked to SIRS, immunosuppression, sepsis and pulmonary infection, free radical-mediated tissue damage, and multi-organ failure.[7] Abundant oxidative stress may compromise the immune system, causing a state of immune suppression and delayed wound healing.[2] This condition makes burn patients more vulnerable to secondary infection risking higher mortality rate.

COMBATING BURN WOUND COMPLICATION

Existing burn management emphasizes on prevention of complication, promotion of healing, and treatment for the complications. Early identification of possibly arising complications is the key to better burn outcomes. The massive inflammatory storm following burns is correlated with a higher incidence of infections, sepsis, organ failure, and mortality.[13] Researchers have longed for sensitive biomarkers with the ability to detect and measure life-threatening

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adverse events, which will greatly advance the burn care and reduce post-burn morbidity and mortality rate. Despite the extensive understanding of burn pathophysiology, there is still no reliable biomarkers that can monitor and predict burn complications.

Burn injury greater than 20% TBSA necessitates immediate fluid resuscitation to abate the possible risk of hypovolemic shock due to massive intravascular volume loss. Appropriate fluid replacement within 2 hours post-burn will ensure adequate organ perfusion, minimize the dysregulated cellular and hormonal responses, reduce mortality rate, and improves overall prognosis.[13] The widely used Parkland equation (4 mL/kg/%TBSA of Ringer Lactate solution) is a simple formula to optimize fluid delivery by preventing deleterious effects of over-resuscitation: pulmonary edema, graft failure, prolonged mechanical ventilation, or compartment syndrome.[14] In contrary, under-resuscitation may also lead to life-threatening conditions such as acute kidney injury, wound conversion, sepsis, multiple organ failure, and mortality.[15]

There are two opinions regarding fluid administration in burn patients. Over-resuscitation theory, known as the "fluid creep" or "hyperdynamic resuscitation", believes that additional fluid more than the estimated Parkland formula is associated with improved survival, less incidence of target-organ damage, shorter hospital stay and ventilator days, and lower mortality rate.[15] On the other hand, Arlati et al. demonstrated that permissive hypovolemia protocol allowed sufficient multi-organ perfusion and effectively reduced multi-organ dysfunction.[16] Older work from Lund and colleagues stated similar result where low volume resuscitation during early post-burn period significantly reduced the incidence of acute renal failure and burn-related edema.[17] Nonetheless, the classic Parkland formula is still adapted until further studies could specify the optimal formula for resuscitation goals.

Ideally, burn patients receive 150% of recommended fluid based on TBSA calculation. However, adjustments are made based on compelling conditions such as the extent of TBSA estimates, presence of inhalation injury, electrical burns, and delayed resuscitation. Hemodynamic parameters such as urine output 0.5 to 1 ml/kg/hour and mean arterial pressure (MAP) should be regularly checked to monitor physiologic manipulation in burn patients.[13] Maintaining fluid balance during aggressive fluid administration is challenging without increasing the risk of fluid accumulation in interstitial place. Therefore, other parameters for monitoring fluid balance were popularized to prevent over-resuscitation; such as intrathoracic blood volume (ITBV), transpulmonary thermodilution (TPTD), and extravascular lung water (EVLW) methods.[18]

Sepsis is another important cause of burn-related deaths. However, its timely recognition remains a challenge. Several biomarkers have been evaluated for their clinical utility in diagnosing septicemia. TNF-α, C-Reactive Protein (CRP), IL-6, IL-4, macrophage colony-stimulating factor, procalcitonin (PCT), and erythrocyte sedimentation rate (ESR) were associated in the development of sepsis.[13] IL-8 expression was found to be significantly elevated following burns, and positively correlated with increased multiorgan failure, sepsis, and mortality.[19] The use of routine corticosteroid and immune-enhancing dietary supplements to suppress inflammation in sepsis also remain controversial in burn patients.[20] However, low dose hydrocortisone was shown to reduce the duration of vasopressor administration in burns with severe shock.[21]

MEDICAL NUTRITION THERAPY IN BURN MANAGEMENT

The outcome of burns depends on the time of treatment. Burn patients experience twice-normal whole-body metabolic rates, excessive protein catabolism, loss of protein and micronutrients through burn exudates, reduced lean body mass, and state of hyperglycemia.[10] These responses are associated with several adverse events within 48 hours post-burn, such as severe cachexia, bacteremia, immune dysfunction, sepsis, and organ failure.[13] Severe burn condition is correlated with decreased dietary intake due to trauma and possible orofacial injury, resulting in nutrient deficiency and malnutrition.[22] Tight glycemic control with adequate dose of insulin was associated with higher survival rate, considering that insulin also provides additional immunomodulatory effects, protects the mucosal and skin barriers, and limits bacterial translocation.[13]

Medical nutrition therapy should be the cornerstone of burn management, considering that hypermetabolism in burn patients will result

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in cascades of dreadful events, including weight loss, muscle wasting, immunosuppression, growth retardation, impaired wound healing, susceptibility to infection, multiorgan dysfunction, and death.[10] Aggressive replacement of essential micronutrients and macronutrients was proven to benefit the outcome and minimize complications. The ultimate goal of proper nutrition therapy is to provide adequate calorie requirement, prevent starvation and nutrient deficiencies, maintain body mass, restore protein loss, and in the end reduce infection rate and promote faster wound healing.[22]

The concept of hyperalimentation is implemented for nutritional maintenance in critically ill burn patients. Nutrient requirements are markedly increased in patients with TBSA exceeding 20%, prior malnutrition, or pre-existing diseases such as HIV/AIDS. The estimated requirement may vary according to patient's age, pregnancy status, organ failure, and presence of infection.[23] Total energy requirement (TER) for burn patients is equal to (1000 kcal x BSA[m2] + 25 x %TBSA) which is proportioned into 60-70% glucose. Increased muscle catabolism requires higher protein intake to aid tissue repair (recommended proportion of 20% to 25% from TER). The benefit of additional lipid requirement is dose-dependent and limited to only 15% of TER to reduce infectious morbidity and shorten hospitalization period.[23]

Nutritional support is better delivered through enteral route; oral, nasogastric and nasojejunal feeding, are the routes of choice. Nutrient intake should be commenced immediately or at least within 24 to 48 hours following burns.[24] Early nutrition initiation will blunt the hypermetabolic state and reduce circulating cortisol, catecholamines, and glucagon hormones. *In-vivo* study by Mochizuki et al. showed that initiation of enteral nutrition 2 hours post-burn significantly reduces hypermetabolism within 2 weeks than the control group fed 3 days post-burn, stressing the benefits of prompt nutrition therapy.[25] Excessive stress response, ischemia, complement activation, ROS, and release of inflammatory cytokines and endotoxins also contribute to intestinal barrier dysfunction.[26] Increased intestinal permeability promotes massive bacterial translocation to distant organs that eventually leads to sepsis, immune disturbance, burn shock, multi-organ dysfunction, and mortality.[10] Therefore, early enteral nutrition is beneficial to maintain gut mucosal integrity, motility, and perfusion, which could prevent subsequent ileus or intestinal hypoperfusion. Early fluid resuscitation and nutrition intake should be taken as preventive approach and personalized for each patient; both are the backbone of burns management.[27]

BURN WOUND CONVERSION AS POOR PREDICTOR OF OUTCOME

Burn wound conversion is the progression of ischemic partial thickness wound into non-viable full thickness wound, thus increasing the portion of third-degree burn. Referring to the conventional depiction of burn zones by Jackson, burn progression happens when the zone of stasis can't be salvaged and thus progresses to necrosis. This progression is dangerous because it often contributes to greater surface area and depth, increasing the risk of complications and mortality within 24 hours.[28] Burn wound conversion is predisposed by local and systemic factors. Infections, tissue desiccation, wound edema, and eschar contributes locally to progress burn wound into necrosis. Systemic homeostasis is also jeopardized following burn injury related to impaired perfusion, metabolic derangements, and suboptimal general health status.[3]

Few studies have investigated several prognostic factors that may progress or regress wound conversion in burn injury. It was initially believed that vasoconstriction compromised tissue perfusion and contributed to its advancement into full-thickness burn.[3] At the same time, peripheral vasodilation induced by an elevated level of inducible nitric oxide synthase (iNOS) upregulated downstream pathway of inflammatory mediators and ROS, which threaten the tissue viability in the stasis and hyperemia zone.[29] The understanding of pathogenesis of wound conversion has evolved greatly, from the well-accepted theories of micro thrombosis, ischemia, and ROS, to the most recent concept highlighting the role of autophagy as a potential determinant behind secondary burn damage.[3,8,28,30] Older works revealed that more apoptotic activity, ischemic cell death, and tissue death were concentrated in the zone of stasis.[28]

Adequate wound debridement, dressings, cytokine- and inflammatory cascade-targeted therapy may also reduce the inflammatory activity in burn wounds. Recent work by Tan and

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colleagues reported that the activity of autophagy and apoptosis in burns occur at different time points, thus augmenting autophagy with rapamycin antibiotic could improve wound healing and lessen burn conversion.[30] The current trend considers that careful approach to this salvageable burn tissue is a breakthrough for new directions in burn management. Controlling burn conversion holds the key to obviate the necessity for surgery while pursuing limited scarring during the healing process.[11]

REVERSING PROGRESSION OF BURN WOUND DEPTH

Progressive expansion of ischemic area to non-viable necrotic tissue has been a major focus of research. Immediate commencement of fluid replacement minimizes incidences of burn shock, burn-related kidney injury, life-threatening electrolyte imbalance, and mortality.[15] A rat model illustrated by Kim et al showed that adequate resuscitation rate (4 to 8ml/kgBW/%burn) prevents prolonged ischemia in burn wounds while suboptimal fluid replacement (<4ml/kgBW/%burn) exacerbates burn wound deepening. The study also demonstrated that over-resuscitation of 6-8ml/kgBW/%burn is correlated with respiratory distress and tissue edema.[31] They proposed that the benefit of resuscitation is varied according to the depth of the initial burn wound. Similar result was reproduced by Carvajal et al, illustrating that burn resuscitation restores and maintains maximal perfusion pressure in pediatric patients, which accelerates spontaneous healing and minimizes wound progression.[32] Despite the importance of fluid therapy in burn management, little is known about the ideal type and volume of fluid, rate of fluid administration, or method of monitoring. No single formula for optimal resuscitation was proven to be superior. Hence, fluid therapy should be carefully administrated and hourly titrated according to physiological response and various clinical outcomes.[33]

Studies on burn conversion were mainly done *in-vivo* using the comb burn model to replicate the zones of burns. The last decade of research has shown growing interest in other local and systemic intervention. Targeting exaggerated inflammatory responses such as TNF-α, IL-6, IL-4, or complement cascades for immunomodulation are considered as a novel approach to halt burn progression. Eski et al. demonstrated that reduced tissue necrosis was observed in both short-term (3-day) and long-term (21-day) follow-up by treating thermal injury with cerium nitrate baths, which was renowned to alleviate TNF-α levels, decrease leukocyte activation, and activate phagocyte activity.[34] Reduced burn conversion was also successfully demonstrated with systemic or local transplantation of mesenchymal stem cells (MSCs) by attenuating burn-induced apoptosis, downregulating pro-inflammatory cytokines, up-regulating anti-inflammatory mediators, relieving oxidative stress, and promoting better vascularization.[35] Early administration of MSCs (30 minutes post-burn) was considered favorable to preserve more vital tissue in the zone of stasis, reaffirming the therapeutic effects of stem cell treatment in burns.[36]

A recent study by Singer et al. elucidated that tadalafil was deemed superior compared to naproxen and N-acetyl cysteine in reducing necrosis in the ischemic zone of a rat burn model.[37] Tobalem and colleagues treated burn wound with erythropoietin (EPO). The anti-inflammatory, angiogenic, and vasodilatory properties of this hormone dose- and time-dependently limited necrosis and burn depth progression by improving vascular perfusion.[38] The authors also suggested that immediate warm water bath after burns decreased ischemia by promoting vasodilation, contradicting to the old belief that hypothermia or cold-water treatment can limit initial cellular injury, protect post-traumatic circulation, and downregulate inflammatory gene expression.[39] Guo et al. also observed the benefit of hydrogen-rich saline on early burn progression following deep burns.[40] Another approach such as hyperbaric oxygen treatment (HBOT), was investigated for its instant anti-edematous and anti-hypoxic relief and has successfully reduced necrosis and improved wound healing in human burn models.[41]

Local wound, care including antibiotics, dressings, and bioactive agents, are used to accelerate wound healing and minimize damage induced by the initial burn injury. Dressings function to create a moist environment, protect the wound from environmental insult or contamination, provide drainage absorption and pain control.[28] Antibiotics are used in addition to silver sulfadiazine to reduce microbial load and prevent infection, especially in deeper wounds. Other mechanisms such as conventional burn excision and eschar removal have not shown

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consistent ability to prevent necrosis in the stasis zone, suggesting other more important cascades responsible in the pathophysiology of wound conversion.[28]

ANTIOXIDANT AS BODY DEFENSE SYSTEM

Thermal injury causes physiological derangement and alters the body response at cellular and systemic level. Recalling the pathophysiology of burn, consequent ischemia and inflammation post-burn lead to overwhelming ROS production and insufficient scavenging system, which are the greatest contributors for the development of burn complications. The level of ROS and antioxidants in the circulation is positively correlated with the severity of burn area.[5] Uncontrolled circulating oxidative stress level along with plummeted inflammatory activity are dreadful and correlated with higher morbidity and mortality rate.[42]

It is natural that the presence of oxidative stress is counteracted by equal synthesis of antioxidants. Antioxidant, considered as the first line of defense mechanism against free radical damage, delays, removes, and prevents oxidation process that may harm target molecules.[43] These scavenger systems are capable of converting the radicals to less reactive form and neutralizing the deleterious effect of ROS to the body. A depletion of antioxidants is correlated with higher disease occurrence and poorer outcomes.[44] Therefore, dietary antioxidants are essential in restoring circulating endogenous antioxidants and suppressing oxidative stress-induced damages. Numerous studies have highlighted the potential role of antioxidants in preventing degenerative diseases-related morbidity and mortality as shown in cancer, coronary heart disease, obesity, type 2 diabetes, Alzheimer's disease, hypertension, cataract, etc.[45, 46]

Antioxidants are generated endogenously or exogenously supplemented in the form of natural and synthetic antioxidants.[43, 44] Endogenous antioxidants can be classified into enzymatic and non-enzymatic compounds, which is further categorized into metabolic and nutrient antioxidants.[45] The endogenous antioxidant enzymes, such as glutathione peroxidase, catalase, and superoxide dismutase, are naturally produced in the body to protect against free radicals-induced cellular damage.[45] Non-enzymatic metabolic compounds are byproduct of metabolism such as lipoic acid, L-arginine, glutathione, coenzyme Q10, uric acid, bilirubin, etc. Nutrient antioxidants can't be produced in the body and thus are supplied through foods, such as fruits and vegetables containing vitamin C (ascorbic acid), vitamin E (tocopherols), vitamin A (carotenoids) and other phenolic compounds.[45,47] The water-soluble antioxidant acts as ROS neutralizer in aqueous phase before initiation of lipid peroxidation while the lipid soluble antioxidant, such as vitamin E, protects the membrane fatty acids from being oxidized. Others, such as beta carotene and carotenoids are believed to protect the lipid-rich tissue from deleterious effect of free radicals.[48] Antioxidants also come in synthetic form, which is chemically synthesized and fortified to food. Butylhydroxyanisole, butylhydroxytoluene, and gallates, are some examples of synthetic antioxidant. It is important to note that avoiding external oxidants source such as cigarette, alcohol, bad food, and stress is as important as taking antioxidant-rich diet.

ROLE OF ANTIOXIDANTS SUPPLEMENTATION IN BURN WOUND CONVERSION

A Deficiency of micronutrients is often found in critically ill patient, which may benefit from administration of trace elements such as antioxidants.[49] Antioxidants supplementation for ill trauma patients; such as burns, sepsis, post-surgical procedure, cancer, or organ transplantation, was associated with better outcome, however its true benefit for routine treatment still remains controversial.[50] Contrary to the previous statement, some studies implied that antioxidant supplementations exert no significant benefit on disease control and in turn may act as pro-oxidant if consumed significantly above the recommended dietary intakes.[45] A Cochrane systematic review reported that administration of antioxidants (beta-carotene, vitamin E, and higher doses of vitamin A) for primary or secondary prevention in healthy and ill patients with various underlying diseases seem to increase mortality.[51]

Antioxidants therapy for burn management has been widely researched at molecular level for its efficacy in restoring circulating antioxidant defenses. Massive decrease in SOD, glutathione, catalase, alpha-

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tocopherol, and ascorbic acid have been documented in burn injury.[7] Inhalation injury is also a contributing factor that accelerates the reduction in plasma antioxidants. Therapies targeted to block the xanthine oxidase activity may alleviate ROS-induce damage by scavenging ROS from the circulation.[22] Thus, antioxidants along with other trace element supplement have been approved for their benefits in accelerating wound healing post-burns, by reducing the risk of pulmonary infection and length of hospital stay.[5] Understanding the role of ROS in the pathophysiology of burn has made antioxidant therapy as a promising step in burns management.

Numerous studies stated that antioxidant supplementations for burn patients significantly promote faster wound healing, shortens hospital stays, reduce mortality rate, and decrease incidence of infection in all cases.[5] A review by Adjepong et al. concluded that administration of trace elements such as vitamin A, C, E, zinc, selenium, and N-acetylcysteine following burn dose-dependently increased the level of circulating antioxidants that was initially scarce up to a normalized level, which is a good indicator for faster recovery.[22] Vitamin E is used to scavenge intracellular free radicals while vitamin C, which is diminished early post-burn, is for scavenging free radicals extracellularly.[52] Early administration of high-dose ascorbic acid may reduce the needed amount of fluid resuscitation, resulting in less tissue edema and more body weight gain.[53] Despite the risk of renal failure following administration of high dose of vitamin C, studies showed that burn areas greater than 20% may gain more benefit from this intervention compared with placebo.[52, 54]

Despite these outstanding outcomes, antioxidant supplementation still requires more exploration through clinical trials, since most of the publications are small-sized research with various dosing and outcome parameters. A pilot study by Raposio et al. evaluated the plasma oxidative stress in partial thickness burns after 2 weeks of antioxidant supplementation and the result showed no significant changes in plasma oxidants level. This finding indicated that the use of antioxidant supplements for medicinal products should be sufficiently evaluated.[55] Individual trace elements should also be explored, as Ross et al. and Berger et al. stated that selenium plays a significant role in immune function and thus is worth a lone investigation of its effect on oxidative stress.[56]

Considering all successful studies about antioxidant supplementation for burn patients, however little is known whether this intervention may have an effect to salvage the stasis zone in burn. A randomized controlled experiment done by Singer et al. on rat models described that administration of curcumin, believed to possess high antioxidant properties, on day 1, 2, 3 post-brass comb-induced burn injury, reduced the burn progression to full-thickness necrosis in the ischemic area.[57] The result showed significant difference between the treated and placebo subjects even on the first day at 30% and 63% respectively ($p=0.003$). The experiment was reproducible and consistent which showed less progression of interspace ischemic area to necrosis following administration of intravenous crude and purified curcumin on day 7 after the burn injury. [58]

Other authors have tried out other sources of antioxidants to minimize free radical damage and prevent burn wound progression through extensive animal studies. Using a rat deep-burn model, Fang et al. also showed that administration of astaxanthin (strong antioxidant element) dose-dependently reduced progression rate in the stasis zone, by suppressing the release of inflammatory mediators and reducing burn-induced apoptosis.[59] Similar result was observed in other studies utilizing N-acetylcysteine (NAC) one hour post-burn and metal chelator disodium ethylenediaminetetraacetic acid (EDTA) containing iron and calcium ions.[58, 60] Enhancing the trace elements zinc and allopurinol were also proven beneficial in combating ROS and enhancing immune function.[22] Topical application of human recombinant copper-zinc SOD successfully salvaged the zone of stasis and promoted better wound healing in burn injury.[61] However, many discrepancies of the study result were found and therefore suggest further investigation for optimal utilization of these agents.

SUMMARY

Abundant oxidative stress and circulating inflammatory cytokines storm following burn has made the wound susceptible to depth progression if not managed adequately. Antioxidant has shown promising standpoints to slow down and counter the toxic implications of free radicals, suggesting that maintenance of adequate antioxidants level is essential in burn

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patients. Administration of dietary antioxidants and trace elements significantly enhanced rate of recovery, prevented complications (infection, sepsis, pneumonia) and reduced mortality rate.[5] Antioxidant supplementations were also proven to prevent burn conversion on the ischemic zone. Future studies are therefore required to translate these promising results from animal studies to real human models. Antioxidant therapy represents a promising avenue to be adjuvant therapy in many clinical conditions, especially for burn management.

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REFERENCES

1. Ruiz-Castilla M, Roca O, Masclans JR, Barret JP. Recent Advances In Biomarkers In Severe Burns. Shock. 2016;45(2):117-25.
2. Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, Natesan S, et al. Burn wound healing and treatment: review and advancements. Crit Care. 2015;19:243.
3. Singh V, Devgan L, Bhat S, Milner SM. The pathogenesis of burn wound conversion. Ann Plast Surg. 2007;59(1):109-15.
4. Auger C, Samadi O, Jeschke MG. The biochemical alterations underlying post-burn hypermetabolism. 2017;1863(10):2633-44.
5. Al-Jawad F, Sahib A, Al-Kaisy A. Role of Antioxidants in the Treatment of Burn Lesions. Ann Burns Fire Disasters. 2008;21(4):186-91.
6. Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman OE, Norbury WB, et al. Pathophysiologic response to severe burn injury. Ann Surg. 2008;248(3):387-401.
7. Nielson CB, Duethman NC, Howard JM, Moncure M, Wood JG. Burns: Pathophysiology of Systemic Complications and Current Management. J Burn Care Res. 2017;38(1):e469-81.
8. Hirth D, McClain SA, Singer AJ, Clark RA. Endothelial necrosis at 1h post-burn predicts progression of tissue injury. Wound Repair Regen. 2013;21(4):563-70.
9. Bittner EA, Shank E, Woodson L, Martyn JJ. Acute and Perioperative Care of the Burn-Injured Patient. Anesthesiology. 2015;122(2):448-64.
10. Rodriguez NA, Jeschke MG, Williams FN, Kamolz LP, Herndon DN. Nutrition in Burns: Galveston Contributions. JPEN J Parenter Enteral Nutr. 2011;35(6):704-14.
11. Horton JW. Free radicals and lipid peroxidation mediated injury in burn trauma: the role of antioxidant therapy. Toxicology. 2003;189(1-2):75-88.
12. Agay D, Andriollo-Sanchez M, Claeyssen R, Touvard L, Denis J, Roussel AM, et al. Interleukin-6, TNF-alpha and interleukin-1 beta levels in blood and tissue in severely burned rats. Eur Cytokine Netw. 2008;19(1):1-7.
13. Snell JA, Loh NHW, Mahambrey T, Shokrollahi K. Clinical review: The critical care management of the burn patient. Crit Care. 172013. p. 241.
14. Tricklebank S. Modern trends in fluid therapy for burns. Burns. 2009;35(6):757-67.
15. Chan J, Ghosh S. Fluid Resuscitation in Burns: An Update:. https://doiorg/101177/10249079090160011 2. 2017.
16. Arlati S, Storti E, Pradella V, Bucci L, Vitolo A, Pulici M. Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. Resuscitation. 2007;72(3):371-8.
17. Lund T. The 1999 Everett Idris Evans memorial lecture. Edema generation following thermal injury: an update. J Burn Care Rehabil. 1999;20(6):445-52.
18. Sánchez M, García-de-Lorenzo A, Herrero E, Lopez T, Galvan B, Asensio MJ, et al. A protocol for resuscitation of severe burn patients guided by transpulmonary thermodilution and lactate levels: a 3-year prospective cohort study. Crit Care. 172013. p. R176.
19. Kraft R, Herndon DN, Finnerty CC, Cox RA, Song J, Jeschke MG. Predictive Value of IL-8 for Sepsis and Severe Infections after Burn Injury - A Clinical Study. Shock. 2015;43(3):222-7.
20. Greenhalgh DG. Sepsis in the burn patient: a different problem than sepsis in the general population. Burns Trauma. 52017.
21. Venet F, Plassais J, Textoris J, Cazalis MA, Pachot A, Bertin-Maghit M, et al. Low-dose hydrocortisone reduces norepinephrine duration in severe burn patients: a randomized clinical trial. Crit Care. 192015.

P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jpr.v7i1.292

22. Adjepong M, Agbenorku P, Brown P, Oduro I. The role of antioxidant micronutrients in the rate of recovery of burn patients: a systematic review. Burns Trauma. 42016.
23. A. Prins RD (SA) M. Nutritional management of the burn patient. http://dxdoiorg/101080/160706582009117 34211. 2016.
24. Mandell SP, Gibran NS. Early Enteral Nutrition for Burn Injury. Adv Wound Care (New Rochelle). 32014. p. 64-70.
25. Mochizuki H, Trocki O, Dominioni L, Alexander JW. Reduction of postburn hypermetabolism by early enteral feeding. Curr Surg. 1985;42(2):121-5.
26. He W, Wang Y, Wang P, Wang F. Intestinal barrier dysfunction in severe burn injury. Burns & Trauma. 2019;7(1):1-11.
27. Natarajan M. Recent Concepts in Nutritional Therapy in Critically Ill Burn Patients. International Journal of Nutrition, Pharmacology, Neurological Diseases. 2019;9(1):4-36.
28. Salibian AA, Del Rosario AT, De Almeida Moura Severo L, Nguyen L, Banyard DA, Toranto JD, et al. Current concepts on burn wound conversion – a review of recent advances in understanding the secondary progressions of burns. Burns. 2016;42(5):1025-35.
29. Rawlingson A. Nitric oxide, inflammation and acute burn injury. Burns. 2003;29(7):631-40.
30. Tan JQ, Zhang HH, Lei ZJ, Ren P, Deng C, Li XY, et al. The roles of autophagy and apoptosis in burn wound progression in rats. Burns. 2013;39(8):1551-6.
31. Kim DE, Uniformed Services University of the Health Sciences B, Maryland, Phillips TM, Uniformed Services University of the Health Sciences B, Maryland, Jeng JC, Uniformed Services University of the Health Sciences B, Maryland, et al. Microvascular Assessment of Burn Depth Conversion during Varying Resuscitation Conditions. The Journal of Burn Care & Rehabilitation. 2019;22(6):406-16.
32. Carvajal HF. Fluid resuscitation of pediatric burn victims: a critical appraisal. Pediatr Nephrol. 1994;8(3):357-66.
33. Bacomo FK, Chung KK. A primer on burn resuscitation. J Emerg Trauma Shock. 42011. p. 109-13.
34. Eski M, Ozer F, Firat C, Alhan D, Arslan N, Senturk T, et al. Cerium nitrate treatment prevents progressive tissue necrosis in the zone of stasis following burn. Burns. 2012;38(2):283-9.
35. Abbas OL, Ozatik O, Gonen ZB, Ogut S, Entok E, Ozatik FY, et al. Prevention of Burn Wound Progression by Mesenchymal Stem Cell Transplantation: Deeper Insights Into Underlying Mechanisms. Ann Plast Surg. 2018;81(6):715-24.
36. Oksuz S, Ulkur E, Oncul O, Kose GT, Kucukodaci Z, Urhan M. The effect of subcutaneous mesenchymal stem cell injection on statis zone and apoptosis in an experimental burn model. Plast Reconstr Surg. 2013;131(3):463-71.
37. Singer AJ, Towery H, McClain SA. Effect of tadalafil on reduction of necrosis in the ischemic zone in a rat comb burn model.: Epub; 2019 [
38. Tobalem M, Harder Y, Schuster T, Rezaeian F, Wettstein R. Erythropoietin in the prevention of experimental burn progression. Br J Surg. 2012;99(9):1295-303.
39. Schaser KD, Stover JF, Melcher I, Lauffer A, Haas NP, Bail HJ, et al. Local cooling restores microcirculatory hemodynamics after closed soft-tissue trauma in rats. J Trauma. 2006;61(3):642-9.
40. Guo SX, Jin YY, Fang Q, You CG, Wang XG, Hu XL, et al. Beneficial Effects of Hydrogen-Rich Saline on Early Burn-Wound Progression in Rats. PLoS One. 102015.
41. Turkaslan T, Yogun N, Cimsit M, Solakoglu S, Ozdemir C, Ozsoy Z. Is HBOT treatment effective in recovering zone of stasis? An experimental immunohistochemical study. Burns. 2010;36(4):539-44.
42. Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. Nature. 2004;429(6990):417-23.
43. Yadav A. (PDF) Antioxidants and its functions in human body - A Review. 2019.
44. Liu Z, Ren Z, Zhang J, Chuang C-C, Kandaswamy E, Zhou T, et al. Role of ROS and Nutritional Antioxidants in Human Diseases Frontiers Physiology. 2018;17(9):477.
45. Pham-Huy LA, He H, Pham-Huy C. Free Radicals, Antioxidants in Disease and Health. Int J Biomed Sci. 42008. p. 89-96.
46. Willcox JK, Ash SL, Catignani GL. Antioxidants and prevention of chronic

P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jpr.v7i1.292

disease. Crit Rev Food Sci Nutr. 2004;44(4):275-95.
47. Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, and diseases. Clin Interv Aging. 132018. p. 757-72.
48. Reddy P, Jialal I. Biochemistry, Vitamin, Fat Soluble. 2018.
49. Berger MM, Oudemans-van Straaten HM. Vitamin C supplementation in the critically ill patient. Curr Opin Clin Nutr Metab Care. 2015;18(2):193-201.
50. Parker R, Rice MJ. Benefits of antioxidant supplementation in multi-trauma patients. Romanian Journal of Anaesthesia and Intensive Care. 2015;22:77-8.
51. Bjelakovic G, Nikolova D, Gluud LL, SImonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database of Systematic Reviews. 2012.
52. Sahib A, Al-Jawad F, Alkaisy A. Effect of Antioxidants on the Incidence of Wound Infection in Burn Patients. Ann Burns Fire Disasters. 2010;23(4):199-205.
53. Rizzo JA, Rowan MP, Driscoll IR, Chung KK, Friedman BC. Vitamin C in Burn Resuscitation. Crit Care Clin. 2016;32(4):539-46.
54. Kahn SA, Beers RJ, Lentz CW. Resuscitation after severe burn injury using high-dose ascorbic acid: a retrospective review. J Burn Care Res. 2011;32(1):110-7.
55. Raposio E, Grieco MP, Caleffi E. Evaluation of plasma oxidative stress, with or without antioxidant supplementation, in superficial partial thickness burn patients: a pilot study. J Plast Surg Hand Surg. 2017;51(6):393-8.
56. Ziegler R, Emory University ACR, Pennsylvania State U, Benjamin HC, Bloomberg School of Public H, caballero@jhu.edu, et al. Modern nutrition in health and disease: Eleventh edition. 2019.
57. Singer AJ, McClain SA, Romanov A, Rooney J, Zimmerman T. Curcumin reduces burn progression in rats. Acad Emerg Med. 2007;14(12):1125-9.
58. Singer AJ, Taira BR, Lin F, Lim T, Anderson R, McClain SA, et al. Curcumin reduces injury progression in a rat comb burn model. J Burn Care Res. 2011;32(1):135-42.
59. Fang Q, Guo S, Zhou H, Han R, Wu P, Han C. Astaxanthin protects against early burn-wound progression in rats by attenuating oxidative stress-induced inflammation and mitochondria-related apoptosis. Sci Rep. 2017;7:41440.
60. Wang CZ, Ayadi AE, Goswamy J, Finnerty CC, Mifflin R, Sousse L, et al. Topically applied metal chelator reduces thermal injury progression in a rat model of brass comb burn. Burns. 2015;41(8):1775-87.
61. Shalom A, Kramer E, Westreich M. Protective effect of human recombinant copper-zinc superoxide dismutase on zone of stasis survival in burns in rats. Ann Plast Surg. 2011;66(6):607-9.

LIST OF ABBREVIATIONS

ACTH - AdrenoCorticoTropic Hormone
CRP - C-Reactive Protein
EDTA - EthyleneDiamineTetraacetic Acid
EPO – Erythropoietin
ESR - Erythrocyte Sedimentation Rate
EVLW - ExtraVascular Lung Water
HBOT - Hyperbaric Oxygen Treatment
IL – InterLeukin
iNOS - inducible Nitric Oxide Synthase
ITBV - Intrathoracic Blood Volume
MAP - Mean Arterial Pressure
MSC - Mesenchymal Stem Cells
NAC - N-Acetylcystein
NF-kB - Nuclear Factor Kappa B Cells
RNS - Reactive Nitrogen Species
ROS - Reactive Oxygen Species
SOD - SuperOxide Dismutase
TBSA - Total Burn Surface Area
TER - Total Energy Requirement
TNF - Tumor Necrosis Factor
TPTD - TransPulmonary ThermoDilution

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