Review Article
Whole body and skeletal muscle protein turnover in recovery from burns

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Abstract: Trauma and critical illness are associated with a stress response that results in increased skeletal muscle protein catabolism, which is thought to facilitate the synthesis of acute phase proteins in the liver as well as proteins involved in immune function. What makes burn injury a unique form of trauma is the existence of vast skin lesions, where the majority of afflicted tissue is often surgically excised post injury. Thereafter, recovery is dependent on the formation of a significant quantity of new skin, meaning that the burned patient requires a large and sustained supply of amino acids to facilitate wound healing. Skeletal muscle has the capacity to store surplus glucose and fatty acids within glycogen and triacylglycerol depots respectively, where glycogen and fatty acids can be mobilized during prolonged periods of caloric restriction or heightened metabolic demand (e.g., exercise), to be catabolized in order to maintain cellular ATP availability. Amino acids, on the other hand, are not generally considered to be stored in such a manner within skeletal muscle, i.e., in a temporary pool independent of structural proteins and cellular organelles etc. Subsequently, in response to severe thermal trauma, skeletal muscle assumes the role of an amino acid reserve where muscle protein breakdown and amino acid release from skeletal muscle serves to buffer plasma amino acid concentrations. Interestingly, it seems like aggressive feeding of the severely burned patient may not necessarily supply amino acids in sufficient abundance to normalize skeletal muscle protein metabolism, suggesting that skeletal muscle becomes an essential store of protein in patients suffering from severe burn trauma. In this article, the effects of burn injury on whole body and skeletal muscle protein metabolism will be discussed in an attempt to distill the current understanding of the impact of this debilitating injury on the redistribution of skeletal muscle protein stores.

Keywords: Burn injury, protein turnover, skeletal muscle, muscle protein synthesis, muscle protein breakdown

Introduction

Severe thermal injury triggers a sustained pathophysiological response which includes, but is not limited to, hypermetabolism, chronic inflammation, marked elevations in peripheral catecholamine and cortisol levels, and severe skeletal muscle wasting [1-5]. While many of these responses to thermal injury enable the body to thermoregulate, combat infection and form scar tissue, they themselves can have a deleterious impact on patient recovery and future morbidity. Indeed, burn injury results in profound cachexia [5], something which is likely compounded by the fact that patients spend prolonged periods of time immobilized post burn [6]. While this depletion of skeletal muscle protein stores negatively impacts the functional capacity and metabolic health of patients recovering from severe thermal injury, it is not without purpose. Following burn injury, when large quantities of amino acids are required, primarily to facilitate the formation of new skin, it seems that skeletal muscle fulfills the role of the body’s amino acid depot [7]. Clearly, while the redistribution of protein from muscle to skin may have catastrophic effects on skeletal muscle mass and function, the closure of skin wounds is of paramount importance to recovery from severe thermal trauma; thus, it seems that skeletal muscle is sacrificed as the body fights for survival. That said, while recognizing skeletal muscles role as an amino acid store in the burned patient, there may be opportunities for
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nutritional and/or pharmacological interventions which stem protein losses while still providing adequate substrates (amino acids) for wound healing. Indeed, several thorough studies have focused on investigating the impact of numerous pharmacological and nutritional interventions on whole body and skeletal muscle protein turnover post burn [8-20]. In this review article, the impact of severe thermal trauma on whole body and skeletal muscle protein turnover, and the role that skeletal muscle plays as an amino acid reserve post burn, will be described and discussed with an aim to offer an accurate description of the impact of thermal trauma on muscle and whole body protein metabolism.

The role of skeletal muscle as an amino acid store

Skeletal muscle represents the bulk of protein within the human body and plays a central role in normal physiological function. Subsequently, changes in muscle mass and/or quality have been implicated in the pathophysiology of numerous diseases (for review see [21]). Unlike glucose and fatty acids, excess amino acids are not stored in independent depots within skeletal muscle in case of temporal reductions in plasma amino acid levels. Rather, excess amino acids in the intracellular compartment of skeletal muscle are incorporated into structural myofibrillar proteins and cellular organelles. Conversely, following even a relatively short period of fasting, skeletal muscle proteins are catabolized in order to buffer plasma amino acid levels. This dynamic relationship between protein synthesis and protein breakdown is generally considered to result in net protein balance in healthy weight stable adults, i.e., protein synthesis is equivalent to breakdown, where skeletal muscle stores turn over at a rate of 1-2 %day⁻¹ [22, 23].

Prolonged ill health or malnutrition results in changes in muscle protein metabolism which lead to decreased muscle mass. In the context of severe malnutrition, skeletal muscle is catabolized in order to provide metabolic substrates for gluconeogenesis and anaploresis [24]. Indeed, it appears that the body adapts to utilizing fatty acids and ketone bodies for energy production while reducing urinary nitrogen excretion in what seems like an attempt to reduce the quantity of amino acids being siphoned towards gluconeogenesis and transamination, or lost in the urine [24]. Despite this, if adequate nutrition is deprived for long enough, death occurs when the whole body nitrogen store is depleted below a critical threshold. By way of example, during the 2nd world war, Jewish Physicians in the Warsaw Ghettos noted that death from starvation, when uncomplicated by other pathologies, occurred when skeletal muscle was no longer able to provide substrates for gluconeogenesis, in what was termed terminal cachexia [25]. Moreover, depletion of body protein stores is associated with death in chronic illnesses such as AIDS and certain cancers [26, 27]. Indeed, when retrospectively evaluating medical records of patients with AIDS in the 100 days preceding death, Kolter and colleagues concluded that death was related to the exhaustion of metabolic substrates, which was attributed to depleted body mass [27]. Moreover, lung cancer is associated with profound muscle wasting, where the degree of cachexia appears to be related to mortality [26]. Subsequently, with the above evidence in mind, it seems that in response to chronic disease or severe malnutrition, skeletal muscle plays an important role in providing substrates (amino acids) for other essential metabolic processes, where the depletion of skeletal muscle protein reserves below a critical level appears to be incompatible with life.

The pathophysiology on thermal trauma

Burn injury, like other forms of trauma results in a sustained inflammatory hypermetabolic state which leads to the dysfunction of numerous organs and physiological systems [1-4, 7, 13, 28-52]. What sets burn injury apart from most other forms of trauma is the existence of large, deep skin wounds. Thus, the severely burned patient is unique in their requirements for amino acids to facilitate wound healing. Profound elevations in skeletal muscle protein breakdown is a hallmark of burn injury [1, 7, 38], where a persistent catabolic state results in the erosion of lean body mass [45]. Given the purpose of this review, perturbations in metabolic physiology and their pertinence to whole body and skeletal muscle protein turnover following burn injury will be discussed in more detail below.

Increased resting metabolic rate seems synonymous with critical illness, but more specifically, burn injury [2, 38, 40, 52, 53]. Indeed, rest-
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...ing energy expenditure in severely burned children has been reported to be up to 100% greater than that of healthy children, where hypermetabolism may persist for several years post burn [2, 40]. The mechanism(s) mediating the hypermetabolic phenotype of the severely burned patients remain to be fully elucidated, however, evaporative heat loss from open wounds is likely to play a role in at least the acute period post injury, where occlusive dressings have been shown to reduce metabolic rate [30, 54]. Further, compromised thermoregulation due to heat radiating from burn and donor wounds likely also contributes to increased metabolic rate post burn [31]. In addition, it seems that chronic adrenergic stimulation is central to the hypermetabolic response in burned patients, where increased cycling of substrates such as fatty acids and glucose appears to increase ATP consumption in burned individuals [50, 51, 57]. Indeed, ATP consuming reactions like gluconeogenesis, protein synthesis and urea production are double that of healthy individuals in patients with large burns [52]. Most strikingly, while extracellular fatty acid cycling doubles in burn patients relative to unburned controls, the rate of intracellular fatty acid cycling is 15-fold greater in severely burned patients when compared to unburned individuals [52]. In support of the suggestion that adrenergic stimulation and substrate cycling mediates the hypermetabolic response to burn injury, there are numerous reports that blocking this pathway with propranolol treatment attenuates the hypermetabolic response associated with severe burns [10, 12, 36, 55].

In addition to perturbations in fat and carbohydrate metabolism post burn, protein metabolism is severely altered by severe thermal trauma. As mentioned above, increased protein synthesis and urea production in burned patients likely play a causative role in the hypermetabolic response to burn trauma [52]. However, increased protein synthesis and urea production are more than likely the consequence of increased whole body turnover, and more specifically, skeletal muscle catabolism post burn. There are numerous reports of marked elevations in skeletal muscle protein breakdown acutely post burn [28, 29, 46, 56], where skeletal muscle catabolism likely stimulates protein accretion in the burn wound [7].

The impact of thermal trauma on whole body protein metabolism

More than two decades of research performed primarily within the Metabolism Unit at Shriners Hospitals for Children – Galveston, under the direction of Professor Robert R. Wolfe, have contributed enormously to our understanding of the impact of thermal injury on protein metabolism. In the late 1980s, these researchers used stable isotopes of urea, leucine, valine and lysine to describe the dynamic response of protein metabolism to burn injury [38]. It was found that elevated protein turnover post injury was associated with hypermetabolism. Further, they showed that protein breakdown remained elevated for several months post injury [38].

In response to burn injury, hepatic gluconeogenesis is elevated in the postprandial state, where alanine [57] and glycerol [50] release from muscle and adipose tissue, respectively, and increased lactate production from peripheral glycolysis [57] are thought to provide substrates for endogenous glucose production. While intracellular fatty acid cycling in adipose tissue and anaerobic glycolysis in skeletal muscle provide glycerol and lactate, respectively, thus preserving endogenous alanine stores, the rate of alanine appearance in severely burned patients is more than double that of healthy individuals [57], suggesting that skeletal muscle catabolism may also play a role in the provision of gluconeogenic precursors. Indeed, when glucose is infused in the post-absorptive state alanine rate of appearance falls in burned patients to levels more or less comparable with healthy individuals [57]. Subsequently, it would appear that in the absence of appropriate glucose provision, alanine appearance in the blood, presumably from skeletal muscle catabolism, serves to provide metabolic substrate for hepatic gluconeogenesis, underscoring the importance of adequate carbohydrate provision for severely burned patients.

While increased alanine turnover in burned patients can be attributed to elevated rates of de novo gluconeogenesis, increased turnover of amino acids such as leucine and arginine have also been reported in severely burned individuals, which are paralleled with increase in whole body protein turnover [58-60].
Importantly, it would appear that whole body protein turnover post burn is the result of both an increase in protein breakdown and protein synthesis. Unlike glucose infusion, which reduced the rate of appearance of alanine from muscle catabolism in burned patients, increasing protein intake acutely post burn, while restoring protein balance to some degree, does not seem to normalize the derangement in skeletal muscle protein metabolism associated with burn injury [61], where protein turnover remained well above levels reported for healthy individuals.

The above observations most likely demonstrate that while increased alanine flux in burned patients may reflect a temporal requirement of the liver for gluconeogenic substrates, chronic increases in whole body protein synthesis and breakdown in severely burned patients permit the redistribution of whole body protein stores, and thus, while transient increases in the nutritional supply of amino acids may mitigate whole body, and in particular skeletal muscle protein losses, they do not resolve the underlying physiological stimulus for elevated protein turnover. In support of this, while burn injury is associated with the erosion of skeletal muscle mass and subsequent changes in body composition [45], we have recently demonstrated that at discharge from hospital, whole body protein turnover is significantly greater in severely burned children compared with healthy children [29]. Interestingly, greater whole body protein turnover in severely burned children seems to result from comparable increases in whole body protein breakdown and synthesis [29]. At first glance these data may be somewhat surprising when considering that severely burned patients remain in a catabolic state with regards to skeletal muscle for several months post injury. However, we believe that

Figure 1. Schematic overview of the proposed redistribution of whole body protein stores in response to severe thermal injury. Red arrows depict the predominant routes of protein redistribution. Bolder arrows depict greater protein efflux/influx.
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this merely reflects redistribution of whole body protein stores, from skeletal muscle to principally skin wounds. This concept is schematically depicted in Figure 1, where we propose that skeletal muscle serves as an endogenous protein source which is mainly disposed of in burn wounds following severe thermal trauma (Figure 1).

The impact of thermal trauma on skeletal protein metabolism

Assuming that the catabolism of endogenous protein stores (skeletal muscle) primarily supports wound healing in burned individuals (Figure 1), it is perhaps not surprising that muscle wasting is more profound in patients with larger burns. For example, phenylalanine loss across the leg of pediatric patients with burns encompassing <40% of total body surface area was approximately 5 nmol min⁻¹ 100 ml⁻¹ of leg volume⁻¹, whereas phenylalanine loss across the leg of patients with larger burns (>40% of total body surface area) was approximately 10-fold greater (approximately 50 nmol min⁻¹ 100 ml⁻¹ of leg volume⁻¹) [62]. In addition, numerous other factors influence the degree of skeletal muscle catabolism post burn. For example, there are stepwise increases in the magnitude of skeletal muscle catabolism with increasing admission weight, time to wound excision, and extent of post burn hypermetabolism [62]. Also, septic patients are significantly more hypermetabolic and catabolic than those who do not develop sepsis [62]. In addition, it also appears that adults are more catabolic than children in response to burn injury [62, 63]. Interestingly, this seems to be the result of a greater compensatory increase in skeletal muscle protein synthesis in response to elevated protein breakdown, rather than a smaller catabolic response in children [63].

Regardless of the mechanism(s) underlying skeletal muscle catabolism in severely burned patients, this adaptive response, while negatively impacting skeletal muscle mass and function, provides amino acids for other essential metabolic processes (Figure 1). Indeed, this concept of redistribution of skeletal muscle protein stores post injury was elegantly demonstrated experimentally in severely burned patients by Gore et al., from our hospital, who employed five compartment modeling of amino acid kinetics in the arterial and venous plasma, vastus lateralis muscle, and skin and burn wounds [7]. Interestingly, the rate of skeletal muscle protein breakdown was very much comparable to the rate of wound protein synthesis. Further, in support of the notion that amino acids derived from skeletal muscle catabolism are disposed of in the burn wound, these investigators were able to show that while there were net losses of phenylalanine from skeletal muscle of these severely burned patients, there was net accretion of phenylalanine in the burn wound despite the fact patients were receiving enteral nutrition throughout the study period [7]. Moreover, the fractional synthesis rate of wound proteins was approximately 5-fold greater than those of skeletal muscle [7], suggesting that amino acid flux into, and presumably their incorporation into constituent proteins of new skin, is greatly accelerated in the burn wound.

A central thesis of this article is that following major burn injury, increased whole body protein turnover reflects the redistribution of protein from skeletal muscle to the evolving burn wound (Figure 1). Interestingly, although there is some disagreement within the literature [56], it seems that skeletal muscle catabolism persists after full wound closure [1, 46], suggesting that even when wounds are considered closed there is still dynamic remodeling of the scar which requires additional protein, something which is likely confounded by follow-up surgeries and therefore subsequent trauma. Naturally, this suggests that the provision of exogenous protein may attenuate or even ablate endogenous (skeletal muscle) protein catabolism. Indeed, Wolfe and colleagues highlighted that exogenous protein provision could at least restore leg protein balance in burned patients, something that was lacking in the post-absorptive state [61]. Furthermore, while phenylalanine rate of appearance, a marker of proteolysis, was not related to protein intake in severely burned patients within the initial two weeks of injury, increased dietary protein intake was associated with higher rates of skin protein synthesis [64]. More recently, in the acute phase, approximately two weeks post injury, the provision of high protein nutrition (above 2.5 g·kg⁻¹·day⁻¹) appeared to diminish skeletal muscle protein losses in children with severe burns [56].
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Although in the acute period post burn, the alterations in skeletal muscle protein turnover, and primarily muscle catabolism may not be readily reversed by increased protein intake, the fact that a less catabolic balance between muscle protein breakdown and synthesis is achieved [61], and that the fractional synthesis rate of skin proteins is increased when dietary protein intake is increased [64], is certainly encouraging. However, it is worth noting these studies were performed within the first two to five weeks post injury. Given that skeletal muscle catabolism persists for at least 9 months post burn [1], this suggests that nutritional support of burn injury, and in particular adequate protein provision, may play an important role in whole body and skeletal muscle protein metabolisms even after wound closure is achieved. Further studies addressing whether protein per se or specific amino acid solutions can augment wound protein accretion or attenuate skeletal muscle catabolism are eagerly awaited.

Summary remarks

Our aim was to distill the current literature pertaining to whole body and skeletal muscle protein metabolism, and to highlight the important role skeletal muscle plays in the pathophysiological response to severe burn injury. Evidence suggests that increased whole body protein turnover following severe thermal trauma reflects the redistribution of the protein compartments in the body, where amino acids derived from skeletal muscle appear to play an important role in protein accretion in skin wounds. While these processes may be an essential adaptation to this catastrophic and unique injury, strategies which attenuate muscle protein breakdown while still providing optimal substrates for wound healing are likely to have beneficial outcomes in burned patients. Exogenous protein or amino acid provision represents a simple intervention which may positively impact the adaption to severe thermal trauma. However, many questions remain as to whether there is an optimal dose and/or composition of amino acids to feed severely burned individuals at various junctures post injury. Answers to the aforementioned questions will likely aid the recovery and rehabilitation of patients afflicted with severe burns.

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Declaration

The authors have no conflicts of interest to report.

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