The Long-Term Impact of Severe Burn Trauma on Musculoskeletal Health

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Severe burn injury causes a profound stress response that leads to muscle and bone cachexia. Evidence suggests that these deficits persist for several months or even years after injury and are associated with growth delay, increased incidence of fractures, and increased hospital admissions for musculoskeletal disorders. Thus, there is an overwhelming need to determine the optimal acute and rehabilitative strategies to mitigate these deficits and improve quality of life for burn survivors. To date, there is limited research on the long-term impact of cachexia on functional performance and overall health, as well as on the lasting impact of pharmacological, nutritional, and exercise interventions. The aim of this review is to emphasize the long-term consequences of musculoskeletal cachexia and determine the best evidence-based strategies to attenuate it. We also underline important knowledge gaps that need to be addressed in order to improve care of burn survivors. (J Burn Care Res 2018;39:869–880)

Mortality after severe burn trauma has decreased significantly over the past few decades; consequently, attention has shifted to the long-term impact of burn trauma on morbidity and quality of life and on the best clinical and rehabilitative practices to hasten recovery of burn survivors. Musculoskeletal disorders, such as muscle and bone cachexia, are prevalent in burn survivors, affecting quality of life and potentially increasing future healthcare costs. However, there is a paucity of research concerning the long-term impact of burn trauma on the musculoskeletal system. The purpose of this review is to draw attention to the magnitude and long-term ramifications of severe burn trauma on the musculoskeletal system while identifying areas where research is currently lacking and to determine the best evidence-based practices to improve muscle and bone health in burn survivors.

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THE METABOLIC STRESS RESPONSE AFTER BURN INJURY

The long-term metabolic stress response to burn trauma includes a hyperdynamic, hypermetabolic physiological reaction that ultimately prolongs morbidity and hinders recovery.[1,2] Burn injury initiates a surge in catecholamines, stress hormones, and inflammatory cytokines that underlay this metabolic response.[3,4] In patients with minor or moderate burns (total body surface area [TBSA] burned < 20%), this effect typically normalizes within a few weeks to months post-injury.[3,5,6] In severe burns, typically those above a 40% TBSA burned, studies report up to a 10-fold increase in catecholamine levels, persistent elevation in stress hormones and inflammatory cytokines, and marked hypermetabolism, all of which can be sustained for 1 to 3 years post-injury.[4,7] This profound hypermetabolic response is proportional to burn size[3] where resting energy expenditure ranges between 120% and 180% above predicted levels and is accompanied by elevated lipid turnover, muscle and bone cachexia, and insulin resistance.[1,4]

The inflammatory hypercatabolic response to severe burn injury

The systemic inflammatory response after burn is characterized by persistently elevated cytokine levels

in children and adults. Several studies have identified a number of pro- and anti-inflammatory cytokines (TNFα, IL-1β, IL-6, IL-4, IL-8, IL-10, IFN-γ, and G-CSF) that are markedly increased for at least 1 month and up to 3 years after burn injury.[4,6,8,9] Elevated cytokine levels appear to be associated with older age and higher burn severity.[3,10] The perturbation in the expressions of these cytokines can lead to compromised immune function, and increased incidence of infection and mortality.[11,12] It is unclear from current knowledge, however, which of these cytokines contribute to cachexia after burn. In patients with cancer, TNFα, IL-1, IL-6, and IFNγ have been identified as working synergistically in the development of cachexia.[13] In particular, TNFα and IL-6 appear to promote cachexia through NF-κB and p38-MAPK signaling pathways, inducing overexpression of inflammation-related molecules and of several proteins in the ubiquitin-proteasome system that are directly involved with muscle wasting.[14,15] Inhibition of the NF-κB pathway or the IL-6 receptor in mice has been shown to be effective against muscle wasting.[16,17] Also, apart from protein degradation, increased activity of NF-κB may impair myogenic differentiation and thus hinder muscle regeneration.[14] In the context of burn, recently published data implicate the ubiquitin-proteasome system and mitochondrial peptidases in muscle catabolism.[18] In regard to the bone, elevated IL-1β and IL-6 levels are known to increase production of the RANK ligand which then promotes bone resorption by stimulating osteoclastogenesis.[19,20]

EFFECTS OF BURN INJURY ON SKELETAL MUSCLE

Muscle Protein Turnover in Burn Patients

Skeletal muscle plays a central role in locomotion, as well as in the homeostasis of whole body protein, lipid, and glucose metabolism. Body protein is in a constant process of synthesis and breakdown.[21] Maintaining skeletal muscle mass is of paramount importance; prolonged depletion of muscle mass and therefore inadequate provision of amino acids (AA) via protein degradation to organs is incompatible with life.[21,22] A constant supply of AA via the bloodstream is vital to the function of a number of organs. Under normal physiological circumstances, this constant supply of AA is achieved through dietary protein intake or skeletal muscle protein breakdown. In healthy individuals, the breakdown of skeletal muscle is in balance with its synthesis, meaning that muscle protein content remains relatively stable over time.

The metabolic stress response to burn injury increases AA needs in various organs. AA are required to support the synthesis of acute phase proteins in the liver, proteins involved in the immune response, and perhaps most importantly to support wound healing.[23] AA requirements in response to burn injury have been estimated to be elevated 4-fold.[21] However, even with aggressive external AA provision, muscle protein catabolism is often unavoidable during the acute response to major burns. Using isotopically labeled AA to trace protein turnover in vivo, it has been estimated that muscle protein net balance for burn patients remains negative even during the fed state.[24,25] Excessive muscle protein breakdown is thought to be the body's response to an increased and unmet AA requirement, which leads to burn-induced muscle wasting.[21]

Interestingly, muscle protein synthesis is also significantly elevated after thermal trauma. Biolo et al found that although protein synthesis was elevated about 50% in burn patients compared with healthy controls, protein breakdown was further elevated by 83%, resulting in negative balance.[26] It is speculated that increased intracellular AA availability from muscle proteolysis saturates intracellular AA levels, driving protein synthesis in the muscle of burned patients. However, this synthetic response is not sufficient to counter elevated muscle protein breakdown rates, leading to net protein loss from skeletal muscle, which can persist for up to 1 year post-burn.[27,28]

Mediators of Altered Protein Metabolism Following Burns

Apart from the excessive needs in AA, other factors, like insulin resistance, elevated stress hormones, and immobilization, exacerbate muscle wasting post-burn; insulin resistance in particular has been associated with higher odds of lean mass loss and increased adiposity in healthy male adults and elderly.[29,30] In patients with cancer, there are indications that impaired glucose tolerance precedes development of cachexia.[31] In burns, a study during acute injury found a correlation between severe hyperglycemia in adults and muscle wasting.[32] In pediatric burn survivors, insulin resistance, a hallmark of the stress response to severe burns, has been shown to persist for up to 3 years post-injury[33] but no studies have investigated whether and to what extend this persistent deficit mediates long-term loss of lean mass and fat accretion. In addition, hypercortisolemia has also been associated with negative muscle protein net balance and subsequent loss of lean mass.[34,35]

Apart from the direct physiologic effects of burn injury on muscle catabolism, severely burned

individuals usually undergo several surgical procedures and an extensive period of immobilization that further exacerbates muscle wasting and results in significant body composition alterations. Lean mass in pediatric burn patients starts declining in the first week of injury.[4] On average, pediatric patients lose from 3% to 10% of total lean mass during their ICU stay, whereas at the same time, fat accretion reportedly increases by 13%.[36,37] Lean mass continues to decline until at least 9 to 12 months post-burn.[27,38] Although a gradual restoration in lean mass can be seen in burn patients in the first year post-injury, particularly in those participating in rehabilitative exercise programs, there is evidence that even after 3 years lean mass remains lower in burned patients when compared with age-matched healthy individuals.[4] Conversely, a study of body composition changes in burned patients did not report significant lean mass changes during the acute phase of injury and up to 24 months post-burn, although there was a trend for lean mass loss within the first 6 months.[39] In this study, the average TBSA was <40%, which may indicate that burn severity is the main predictor of lean mass decline. Because even a 10% loss of lean mass may increase the probability of complications and hinder wound healing,[22] it is imperative that further studies evaluate the magnitude and duration of burn-induced muscle wasting and determine optimal interventions for recovery, especially for adults and elderly where research is minimal.

Functional Impact of Burn-Induced Muscle Cachexia

Studies show that cancer cachexia is an independent predictor of reduced quality of life[40]; muscle wasting leads to limited functional capacity and participation in daily activities, and increased fatigue and psychological distress.[40] For burn trauma, there is a paucity of data concerning the long-term impact on skeletal muscle mass and function; however, there is some evidence of prolonged morbidity related to muscle cachexia following severe burns. In a cross-sectional study of 98 burn survivors questioned on average 17 years after injury, more than 50% reported that they experienced fatigue, limited motion, and difficulties in self-care.[41] In a study of self-reported health at 1 to 2 years after burn, although the mental aspects appeared to have a greater impact on survivors' quality of life, both physical and mental dimensions were below the reference group at all time points.[42] There is not enough evidence currently to evaluate to what extend loss of muscle mass contributes to these persistent functional deficits and to subsequent psychological burden.

Perhaps the most common and evident adverse effect of muscle wasting is the loss of strength and endurance. In burned adults studied at least 6 months post-injury, muscle function, assessed from peak torque, total work, and power, was found to be significantly reduced compared with uninjured controls.[43,44] Similarly, Alloju et al measured strength of the quadriceps muscle group in 46 unburned children and 33 severely burned children at 6 months post-burn; the unburned cohort had 68% and 64% higher peak torque and total work values, respectively, when compared with the burn group.[45]

Since burn-induced muscle wasting in conjunction with prolonged immobilization leads to diminished muscle strength, the question that arises next is what happens once the biologic factors that cause atrophy return to normal and proteolysis subsides. It seems that muscle weakness persists well after wound healing. In the study of St-Pierre et al, participants' muscle function was measured at least 1 year—and on average at 38 months—post-burn and showed that muscle strength remained significantly depressed compared with uninjured controls.[43] In the same study, patients with less severe burns however (TBSA < 30%) appeared to have regained muscle peak torque and power at that time,[43] indicating that burn severity is associated with the extent of initial muscle deconditioning and subsequent recovery. Recent evidence suggests that even when muscle regrows after critical illness, it may have lost its regenerative capacity and thus remain weak.[46] In light of these findings, it is of paramount importance to prevent muscle mass and strength loss as well as to restore muscle function early in the rehabilitative process.

EFFECTS OF BURN INJURY ON BONE

Effects of Burn Injury on Bone Turnover

The bone is a complex and dynamic tissue that is constantly remodeled, undergoing continuous resorption and formation. Remodeling is necessary to replace and repair micro damage, shape the skeleton during growth, and regulate calcium metabolism. Control of this process depends on several signaling pathways that are regulated by the parathyroid hormone (PTH), growth hormone, Vitamin D, calcitonin, steroids, and cytokines such as RANKL[47] which are disrupted following burn injury.[4,7] Severe burn injury distorts bone homeostasis by initially increasing bone resorption and inhibiting bone formation.[48] For at least 3 months post-burn, increased circulating glucocorticoid levels lead to a prolonged stage where little bone formation occurs, whereas

resorption persists.[48] Following acute bone resorption in burn patients, the bone becomes hypodynamic with decreased bone turnover.[49]

There are several suggested mechanisms that could result in this altered sequence of bone remodeling. First, subsequent to the hypermetabolic response previously described, the increase in proinflammatory cytokines IL-6 and IL-1β signals osteoblasts to secrete RANKL, whose main function is to activate osteoclast differentiation leading to increased osteoclastogenesis and bone resorption.[49] Another mechanism that distorts bone metabolism is the sustained increase in glucocorticoid secretion that further increase RANKL production.[48] At the same time, elevated cortisol levels enhance osteoblast apoptosis, reducing the rate of bone formation.[49] Finally, immobilization further aggravates bone resorption[49]; although the mechanism is not entirely understood, it is clear that the subsequent skeletal unloading negatively affects formation and bone strength.[49,50] To what degree muscle mass loss exacerbates the loss of bone mass and quality after burn is unclear, but there is evidence that increase in bone mass follows approximately 3 to 6 months after lean mass improvement.[51,52]

The first indication that severe burn injury was associated with reduced bone formation and mineral apposition rate in humans was identified in 1993 through iliac crest bone biopsies conducted in adults with severe burns.[53] Two years later, the findings of decreased bone formation biomarkers were also confirmed in a study of pediatric burn patients.[54] It has now been well established that within the first weeks of severe burn injury, bone mineral density (BMD) and bone mineral content (BMC) start to decline because of immobilization, increased glucocorticoid levels, and inflammatory cytokines' production. There are indications that this decline is more pronounced in children than adults and continues for at least 6 months to 1 year after hospital discharge.[7,38,39] Regarding the magnitude of this decline, it has been reported that as early as 1 month post-burn, 71% of adult patients had distal forearm bone density reduced below the 16th percentile for age and gender.[55] For lumbar spine measurements, this percentage was 43%.[55] In a recent cross-sectional study conducted in male adults in Iran 6 to 12 months after injury, only 26% of burn patients had normal lumbar bone density compared with 86% of matched controls.[56] The prevalence of lumbar osteoporosis in the burn group was 25%, whereas 49% were osteopenic, compared with 0% and 14%, respectively, in unburned controls. Interestingly, TBSA in this group ranged from 5% to 40% and was found to be inversely associated with BMD, indicating that in adults physiological effects on bone health may not be limited to major burns, but are proportional to burn severity.[56]

A gradual increase in BMD and BMC has been reported after the first year post-burn; however, these remain significantly lower than those of healthy controls.[38,39] In a cross-sectional study by Klein, 60% of burn survivors remained osteopenic at a mean of 5.5 years after injury.[57] In a large pediatric cohort study of 977 patients from Shriners Hospital in Galveston, it was reported that BMC remained below the average for healthy unburned children at 3 years post-injury, although BMD was not statistically different from normal throughout the recovery period. Despite BMD being similar between the two groups, burned children had smaller bones and lower BMC. Whether this is the result of smaller stature or an indication of biomechanical changes in bone strength leading to increased fracture risk is unclear. Caution is required in interpretation as the two groups in this study had significantly different height and weight values. In contrast, in a prospective randomized trial that used *z*-scores for assessing changes in BMD over time, burn children's bone density deteriorated for at least 1 year, declining from −1 standard deviation below the mean at discharge to −2.1 on average at 12 months.[52] Discrepancies in the results of these two studies can likely be attributed to the use of different control groups; although the use of population *z*-scores reduces potential bias in the selection of the healthy cohort, there is a paucity of available data on non-U.S. pediatric populations. Thus, a major challenge for pediatric research is that the inadequacy of appropriate population race, age, and sex reference values prevents comparison between different groups or studies and limits the generalizability of findings.

Long-Term Impact of Burn Injury on the Skeleton

Alterations in bone metabolism are also associated with growth arrest, particularly in burned children. In a prospective study following 80 pediatric burn survivors, height delay was present for 3 years post-injury in males.[58] Seventy percent of females remained below normal height at 3 years post-injury compared with 55% at admission, but the difference was not statistically significant.[58] In a more recent study of pediatric burn patients, age and sex-adjusted height scores were significantly lower than expected from standard growth curves after 5 years.[59] Almost 11% of the population had indications of stunting.[59]

The duration, magnitude, and long-term health impact of altered bone metabolism remains unclear and underappreciated. Chronically reduced BMD could lead to diminished peak bone mass, a major determinant in the risk for osteoporosis in adult life.[50] A cross-sectional study of 68 patients found a two times higher prevalence of post-burn fractures in children with TBSA > 40% compared with what is nationally reported.[57] In a recent study of 13,244 survivors that sustained burns during childhood, hospital admissions for bone density disorders up to 32 years later were 4.5 to 5.6 times higher than non-burn controls.[60] Also, cumulative length of hospital stay for these disorders was on average 17 times as long for previously burned patients. Even more unfavorable long-term outcomes have been reported for burns sustained during adulthood, where survivors were 14 times more likely to be admitted for bone disorders compared with age and gender-matched controls.[61] Although these latest findings come from retrospective studies with several limitations, it becomes clear that the effects of burn on bone health are persistent and perhaps even lifelong; the impact on survivors' quality of life and the financial burden imposed can be grave but has only recently began being explored.

PHARMACOLOGICAL STRATEGIES TO ATTENUATE MUSCLE AND BONE CACHEXIA FOLLOWING BURN TRAUMA

Testosterone Therapy

The testosterone analogue oxandrolone has been used experimentally to treat weight loss due to trauma or chronic disease. Because oxandrolone causes fewer androgenic adverse effects than other testosterone esters and can be administered orally, it is usually preferable to other testosterone analogues. In a study of pediatric burn patients who received oxandrolone during the catabolic phase, approximately 1 week after admission and for the duration of hospital stay, lean mass was preserved; in contrast burn controls lost ~10%.[37] The mechanism through which oxandrolone may preserve lean mass has not been studied in adults; in children isotope tracer studies showed that oxandrolone-treated patients had improved protein net balance after 1 week, possibly attributable to increased protein synthesis.[62] With longer administration, oxandrolone seems to restore the muscle's response to anabolic stimuli, like external AA provision, and thus improve net balance.[63] In adult patients, 6 months of oxandrolone administration during rehabilitation led to ~ 5% increase in lean muscle mass compared with controls, which was retained for an additional 6-month period after treatment discontinuation[64] (Table 1). The rate of weight and lean mass gain in the adults is not dependent on age; a group of adults with a mean age of 60 years showed similar improvements as a younger adult group when treated with this agent.[65]

Randomized studies of pediatric burn patients, who received 0.2 mg/kg/day of oxandrolone for 12 months, showed improvement in lean body mass (LBM) and BMC compared with placebo.[66] These improvements range from 10% to 13.5% for LBM and are approximately 12.5% for BMC.[51,52] For BMD, oxandrolone-treated children had *z*-scores ranging from –0.7 to –1.0 at 12 months, whereas for control patients, the average score was –2.1.[52] When combined with a 12-week exercise program, oxandrolone further improved lean mass accretion by ~ 7% compared with oxandrolone alone[67] (Table 1). Even at 5 years post-burn, benefits in bone content accretion were evident in the group treated with oxandrolone for 1 year vs placebo.[66] When the treatment was given for 2 years, bone improvement was even greater than 1 year administration[68] (Table 1). In patients during growth spurt years (7 to 18 years), bone content and density begun improving sooner and thus oxandrolone provided longer lasting benefits.[66,68] Oxandrolone can modestly enhance collagen production in vitro which may offer an explanation for the improvements in bone that it exerts[69]; however, it is speculated that at least in the first year after injury these gains are mainly driven by the increase in lean mass and skeletal loading.[52,66]

Oxandrolone appears to be a promising agent for restoring musculoskeletal health after burn injury. According to a recent meta-analysis, it also appears to be safe, with limited adverse effects.[70] However, it is worth noting that the aforementioned studies are single-centered and predominantly from a single hospital focusing on the treatment of burned children; multicentered clinical trials studying the effectiveness and safety of oxandrolone in both burned children and adults are needed.

β Blockade

The hypermetabolic response to burn injury is primarily mediated and propagated by a 10-fold increase in catecholamine levels. Propranolol is a nonselective β-blocker that inhibits catecholamine binding to β-adrenoreceptors and thus moderates burn-induced hypermetabolism. Reduction in heart rate and resting energy expenditure are the more common effects of propranolol administration in burned individuals.

In a large randomized trial of 179 pediatric patients, propranolol administration at a mean rate of 4 mg/kg/day for 12 months improved the hypermetabolic response, led to a 23% decrease in central fat deposition, and to 10% higher accretion of peripheral lean mass compared with the placebo group[71] (Table 1). In addition, propranolol patients were less likely than the control group to lose BMC at 6 months after drug initiation.[71]

Propranolol likely improves lean mass by stimulating protein synthesis.[72] Thirteen patients were randomized to receive propranolol during acute hospitalization, whereas 12 patients received placebo. Protein kinetic studies conducted 2 weeks later showed that propranolol-treated patients had increased protein synthesis efficiency, whereas their breakdown rate did not differ from controls; therefore, propranolol resulted in net protein balance after 2 weeks of administration and in a subsequent 6% lean mass increase at discharge (Table 1). It remains unclear whether propranolol actually directly stimulates myofibrillar protein synthesis or if propranolol's effects on the hyperdynamic response to burns mediate this response.

Combined Oxandrolone and Propranolol Therapy

Because of the anti-inflammatory properties of propranolol, it is possible that it may act synergistically with oxandrolone in further improving muscle anabolism and protein synthesis. In fact, Herndon et al showed that combined administration of these two agents for 1 year resulted in improved growth rate compared with patients taking placebo or one of the drugs only.[73] In addition, growth arrest lasted on average 84 days less for this group compared with controls.[73]

Hypotension, bradycardia, and insulin resistance have been reported as adverse outcomes of propranolol use, but overall it is considered a safe pharmacological agent.[74] β-Blockers have also been associated with decreased exercise capacity and muscle fatigue; however, in a randomized trial of 62 children recovering from burns, propranolol in addition to exercise showed similar improvements in muscle strength and lean mass as exercise alone.[75] Overall, there is evidence that propranolol positively affects metabolic rate, cardiac, and liver function and also benefits the musculoskeletal system.[74] However, this evidence comes predominantly from pediatric studies; only two short-term studies have been conducted in adults, with small sample sizes and limited outcomes examined. Given that more than 60% of burn centers regularly use propranolol in children and adult cases, it is essential that more studies are pursued, preferably multicenter and in the adult population.[76]

Recombinant Human Growth Hormone Therapy

Recombinant human growth hormone (rhGH) has been used to modulate the post-burn hypermetabolic response and promote wound healing, possibly by enhancing hepatic production of IGF-1 and augmenting collagen synthesis. Randomized placebo controlled trials in convalescent burn children have shown that provision of 0.05 mg/kg/day of growth hormone up to 1 year positively affects lean mass, height velocity, bone content, and serum levels of IGF-1.[77,78] However, although height percentiles continued improving significantly more for growth hormone patients compared with controls even after 12 months from treatment discontinuation, the rate of lean mass accretion was not sustained.[79] In a study of various doses of growth hormone treatment in burn children, optimal results for muscle mass were obtained at a dose of 0.2 mg/kg daily for 24 months.[80] Interestingly, although provision of 0.05mg/kg of rhGH daily resulted in significant improvement in BMC , higher doses had a negative impact, despite increased skeletal loading (Table 1). This indicates that higher levels of rhGH may stimulate bone resorption and suppression of the parathyroid hormone.[80]

In adult burn patients, growth hormone studies are limited. Kim et al showed that administration of 2 mg of sustained release rhGH per week for 3 months during rehabilitation was sufficient to improve lean mass by 6% more than controls[81] (Table 1). BMC showed no improvement during this time period.

In regard to safety, there is evidence that growth hormone leads to increased morbidity and mortality in adults with critical illness.[82] In burn patients, adverse outcomes reported have been minimal and restricted to hyperglycemia and glucose intolerance.[80] Because the majority of growth hormone studies in burn patients are conducted in children, it is likely that severe adverse effects manifest with advancing age.

Bisphosphonate Therapy

Pamidronate is a long acting bisphosphonate that acts as an antiresorptive agent to attenuate bone loss. In burn patients, only one study has been conducted using this agent, with very promising results. In this randomized pediatric trial, pamidronate (1.5 mg/kg)

was administered parenterally within the first 10 days of injury and again 1 week later and significantly prevented BMC loss for 6 months compared with placebo.[83] In fact at 6 months, the pamidronate group had approximately a 15% increase in lumbar BMC compared with a decrease in controls and this therapeutic effect was sustained even at 24 months post-burn[83,84] (Table 1). Pamidronate completely prevented loss of mineral content from the bone and resulted in significantly improved bone density *z*-scores, albeit still lower than age and sex matched population values.[84]

A subgroup of the pamidronate and placebo-treated patients were also enrolled in tracer infusion studies for evaluation of muscle protein kinetics. Surprisingly, the pamidronate subgroup (10 patients) had lower muscle fractional synthesis and breakdown rates that resulted in positive net protein balance, whereas in the placebo group (7 patients), protein balance was negative.[85] Pamidronate is thought to preserve bone by hindering osteoblast apoptosis owing to increased glucocorticoids' production. However, it does not seem to affect the inflammatory response to burn injury or decrease catabolism.[85] Therefore, the mechanism through which pamidronate improved muscle protein kinetics remains unknown and warrants further investigation.

Insulin Therapy

In a randomized trial conducted in 186 children with burns, tight glycemic control (glucose levels maintained between 80 and 110 mg/dl), achieved through continuous insulin infusion during acute injury, resulted in improved lean muscle mass and BMD at time of discharge, compared with a less strict protocol where glucose was maintained between 140 and 180 mg/dl.[86] Lean mass gains averaged 9%

Table 1. Effects of pharmacological interventions on lean body mass, fat mass, bone mineral content, and bone mineral density in burn children and adults

	Lean Mass	Fat Mass	BMC	BMD
Oxandrolone (children)				
0.2 mg/kg/d in acute[34]	~17%↑	Ns	ns	ns
0.2 mg/kg/d for 1 y[62]	ns		~22%–60%↑	ns
0.2 mg/kg/d for 1 y[47]	~12%↑		~10%↑	
0.2 mg/kg/d for 1 y[48]	~12%↑		~13%↑	
0.2 mg/kg/d for 2 y[64]	↑*		↑*	↑*
Oxandrolone (adults)				
20 mg/d until 80% weight restored[60]	5%↑			
Oxandrolone + exercise (children)				
0.2 mg/kg/d for 1 y[62]	~20%–50%↑		↑*	ns
0.1 mg/kg/d for 1 y[63]	12.8%↑			
Propranolol (children)				
4 mg/kg/d for 1 y[67]	9.5%↑	23%↓	↑*	↑*
1.98 mg/kg/d in acute[68]	~6%↑			
Pamidronate (children)				
2 doses of 1.5 mg/kg[79]			~9%↑	
Insulin (children)				
Target glucose between 80 and 110 mg/dl in acute[82]	~9%↑	~17%↑		~4%↑
Target glucose between 100 and 140 mg/dl in acute[83]	~20%↑	ns	~15%↑	
Growth hormone (children)				
0.05 mg/kg/d for 1 y[74]	20%↑			
0.05 mg/kg/d for 1 y[75]	~18%		~20%–50%	
0.05 mg/kg/d for 1 y[76]	ns	ns	~25%↑ at 1 y	
0.1 mg/kg/d for 1 y[76]	~12%↑ at 1 y	~3%↓ at 1 y	ns	
0.2 mg/kg/d for 1 y[76]	~14%↑ at 1 y	~2%↓ at 1 y	~4%↓ at 1 y	
Growth hormone (adults)				
2 mg/wk for 3 mo[77]	~6.5 %↑	ns	ns	

ns, not significantly different.
↑, Percent increase compared with controls when data available.
↓, Percent decrease compared with controls when data available.
↑*, Significant increase compared with controls, data for percent calculation not available.
~, Estimated from figures when values not available.

and bone density improved 4% in this period. Similar results were shown in another small trial of pediatric patients who were treated with continuous intravenous insulin titrated to maintain glucose levels between 100 and 140 mg/dl[87] (Table 1). A study on management protocols of hyperglycemia in the same population showed that less tight glycemic control, with insulin administration once glucose exceeded 180 mg/dl, resulted in improved and sustained lumbar BMC compared with patients without hyperglycemia that did not receive insulin during the acute phase of injury.[88]

Insulin modulates hyperglycemia, another hallmark of the post-burn response, by stimulating glucose uptake by muscle and adipose tissue. At the same time, as Sakurai et al showed, exogenous insulin infusion can increase protein synthesis and result in positive net balance.[89] In this study of predominantly adult participants, insulin was administered continuously for 7 days along with enteral nutrition. At the end of the study, muscle protein kinetics were improved after insulin treatment. Although both fractional synthesis and breakdown rates increased, overall net balance was positive, driven by a remarkable 6-fold elevation in AA uptake from blood.[89] Insulin also seems to have an anabolic effect on bone; it is essential for osteoblast differentiation and may play a role in osteocalcin production, but evidence of such mechanisms is still extremely limited.[90]

In a randomized trial of 1548 adults, intensive insulin therapy improved morbidity and mortality, mainly by reducing cases of multiorgan failure due to sepsis.[91] However, there are also arguments against tight glycemic control with insulin, since it can lead to hypoglycemia and other adverse effects, such as renal failure.[92] Given that other studies in severely ill patients have not corroborated the benefit of insulin on mortality, the optimal target range for glucose control remains unclear. In burn patients, no differences in mortality have been attributed to insulin, but the considerable risk of hypoglycemia has shifted attention to other potential drugs with similar effects.

Metformin is a biguanide that is known to reduce hepatic gluconeogenesis while increasing peripheral glucose uptake. Unlike insulin, hypoglycemia is not associated with metformin therapy. This has made metformin an attractive alternative to insulin in the burn ICU. Adult burn patients treated with metformin were shown to need significantly less insulin to maintain normal glucose levels compared with insulin-treated patients; at the same time, the risk of hypoglycemia was significantly lower for the metformin group.[93] Studies are limited though and there is no definitive evidence on the effects of metformin on skeletal muscle and bone mass. One study of 13 pediatric patients demonstrated that metformin improved anabolism, by stimulating muscle protein synthesis after 1 week of administration, without any adverse effects.[94] However, in a recent study of rehabilitating burn children that compared short-term metformin coupled with exercise versus exercise alone, no additional benefit of metformin on muscle strength, endurance, and glycemic control was evident.[95] Other potentially useful agents, such as fenofibrate, a PPAR-α agonist, have been proposed to address insulin resistance after burns, but research is still limited to small single-center trials. Larger long-term studies that focus on clinical endpoints are needed to assess the potential of these agents in treatment of burn patients.

THE ROLE OF NUTRITION AND EXERCISE IN MITIGATING CACHEXIA AND RESTORING MUSCLE AND BONE MASS IN SEVERELY BURNED PATIENTS

Early initiation of enteral feeding can mitigate muscle catabolism and decrease the incidence of sepsis and inflammation.[96] Determining the optimal nutritional intake and substrate composition is however a challenging task. Although adequate nutrition is necessary to attenuate muscle loss, overfeeding has been associated with poor outcomes, such as prolonged ICU stay, hyperglycemia, and fatty liver.[97,98]

According to established research, protein provision at a rate of 1.5 to 2.0 g/kg/day is recommended for attenuating the burn catabolic response in adults and improving muscle mass and function.[99,100] Higher protein intake does not further stimulate protein synthesis.[101] Children have greater protein requirements than adults due to growth; therefore, higher protein intake has been advocated as beneficial to wound healing; however, there is an associated risk of increased urea production when consuming high protein amounts without any further benefit in protein metabolism and lean mass.[102] In terms of nutritional composition, several burn centers follow a high carbohydrate, low fat diet (82% carbohydrate, 15% protein, and 3% fat) after it was shown to improve protein balance by reducing breakdown when compared with a high fat diet.[103] However, this was a single-center trial with only 14 participants and without long-term follow up; there is a need for multicenter prospective nutritional studies in burn injury.

Multivitamin supplementation is also required after burn injury, since vitamin and trace elements' deficiencies are evident within a few days of trauma.[97] The optimal dosage, timing, and duration, in order to mitigate muscle and bone loss, however, remain inconclusive. Klein et al measured serum 25(OH)D levels in 11 patients at 7 years after burn.[104] Only one patient had values at the normal range; the rest were vitamin D depleted. Low circulating levels of 25(OH)D were also associated with low BMD values for gender and age, indicating that vitamin D insufficiency has a role in bone mass erosion.[104] However, no study has been able so far to identify an adequate dose or duration of vitamin D supplementation to positively affect BMD and BMC development.[105–107]

Resistance exercise programs have been shown to be efficient in improving muscle mass and strength in the rehabilitative stage of injury without aggravating hypermetabolism.[108,109] In a 12-week in-hospital supervised resistance training program incorporating aerobic conditioning that was initiated at 6 months post-burn, pediatric survivors improved lean muscle mass by 6.4% on average compared with the non-supervised home patients.[110] Muscle strength, measured by peak torque and work capacity, was also significantly elevated in the hospital exercise group. In addition, a further study showed that 3 months after cessation of the exercise program lean muscle mass continued to improve in the exercising patients at a significantly higher rate than nonexercising.[111] Similar beneficial effects of supervised exercise programs on skeletal muscle health have been reported in adults with healed burns.[44] In this study, burn survivors randomized to a 12-week isokinetic training program improved their muscle strength to levels comparable to uninjured individuals, whereas the no-exercising group maintained significantly lower values.[44] These findings underscore the importance of including exercise training as part of outpatient burn rehabilitation in order to restore muscle function.

An interesting exercise modality that appears to be beneficial to the bone in nonburned children is vibration exercise. In burns only one study has assessed the effectiveness of a 6-week vibration program in addition to resistance exercise (Rex) on bone structure.[112] The program was initiated at discharge from ICU and participants were randomly allocated to receive Rex or Rex plus vibration exercises. Whole body BMC decreased in both groups after 6 weeks, but the decrease in the second group was significantly less. Truncal and leg bone density were not altered in the vibration+ Rex group, whereas they were reduced in the Rex patients.[112] It appears that vibration exercise may preserve bone mass, but longer periods of study are needed to establish potential benefits.

Exercise training can also provide psychosocial benefits to burn survivors. Grisbrook et al showed that a 12-week training program can improve health-related quality of life scores, especially those associated with body image and physical function.[113]

A recent meta-analysis on the effects of resistance training during burn rehabilitation found no significant overall improvement in lean muscle mass or muscle strength.[114] Although this result may seem surprising, it is rather a reflection of the limitations of current burn rehabilitation research; among the studies included in the meta-analysis, nine involved children and only two adult patients. Sample sizes were small, ranging from 20 to 40 patients, increasing heterogeneity. Exercise protocols also varied among studies, as well as outcome measurements. It becomes clear that to develop the optimal evidence-based recommendations for burn patients, further studies are needed that would ideally employ standardized techniques and measurements.

SUMMARY

Within the first few weeks after severe burn injury, loss of muscle and bone mass becomes a significant clinical challenge, which hinders recovery. Muscle wasting in particular can increase the acute risk of infections, delay wound healing, and complicate rehabilitation. This decline in musculoskeletal mass persists for at least 3 to 6 months and despite gradual improvement afterwards, burn survivors may not completely regain normal muscle and bone mass for several years. This persistent deficit leads to severe long-term, or even lifelong, implications; loss of muscle strength, fatigue, and difficulties in executing daily activities negatively affect quality of life. Moreover, burn survivors are more prone to fractures and bone density disorders as well as to lengthier and more frequent hospital admissions that dramatically increase the overall disease burden. Furthermore, burn patients undergo a prolonged period of metabolic shock and exhibit persistent insulin resistance and altered body composition even for several years post-injury that could potentially increase the risk for diabetes, osteoporosis, or other chronic conditions in this population. As the use of national administrative healthcare datasets for research purposes expands, a great opportunity arises to answer such questions and fully evaluate the lifelong impact of severe burn injury.

Attenuation of lean mass and bone loss during the acute phase of injury is imperative; a combination of adequate nutrition, exercise, and drugs is warranted. Several pharmacological agents have been investigated in the past decades; there is strong evidence that oxandrolone benefits the musculoskeletal system; however, evidence remains inconclusive or weak for the remaining drugs, mainly due to lack of large cross-national trials with adequate follow-up. The potential synergistic effects of early exercise initiation, continuous nutritional support, and drug interventions that continue throughout rehabilitation need to be further investigated in order to shape the optimal intervention for these patients.

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