Review Article on Pediatric Critical Care

A narrative review of skeletal muscle atrophy in critically ill children: pathogenesis and chronic sequelae

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Muscle wasting is now recognized as a growing, debilitating problem in critically ill adults, resulting in long-term deficits in function and an impaired quality of life. Ultrasonography has demonstrated decreases in skeletal muscle size during pediatric critical illness, although variations exist. However, muscle protein turnover patterns during pediatric critical illness are unclear. Understanding muscle protein turnover during critical illness is important in guiding interventions to reduce muscle wasting. The aim of this review was to explore the possible protein synthesis and breakdown patterns in pediatric critical illness. Muscle protein turnover studies in critically ill children are lacking, with the exception of those with burn injuries. Children with burn injuries demonstrate an elevation in both muscle protein breakdown (MPB) and synthesis during critical illness. Extrapolations from animal models and whole-body protein turnover studies in children suggest that children may be more dependent on anabolic factors (e.g., nutrition and growth factors), and may experience greater muscle degradation in response to insults than adults. Yet, children, particularly the younger ones, are more responsive to anabolic agents, suggesting modifiable muscle wasting during critical illness. There is a lack of evidence for muscle wasting in critically ill children and its correlation with outcomes, possibly due to current available methods to study muscle protein turnover in children—most of which are invasive or tedious. In summary, children may experience muscle wasting during critical illness, which may be more reversible by the appropriate anabolic agents than adults. Age appears an important determinant of skeletal muscle turnover. Less invasive methods to study muscle protein turnover and associations with long-term outcome would strengthen the evidence for muscle wasting in critically ill children.

Keywords: Muscle protein synthesis (MPS); muscle protein breakdown (MPB); critically ill children; muscle turnover

Submitted Sep 17, 2020. Accepted for publication Dec 18, 2020.
doi: 10.21037/tp-20-298
View this article at: http://dx.doi.org/10.21037/tp-20-298

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Introduction

Concerns of reduced function and physical impairment in critically ill children following pediatric intensive care unit (PICU) stay have increased in the past few years (1,2). This has prompted the study of interventions, such as early mobilization, in reducing long-term impairments (3,4). In critically ill adults, similar observations of functional impairment have been reported, attributable to acute muscle wasting that occurs during intensive care unit (ICU) stay (5,6). Muscle wasting in critically ill adults is increasingly recognized as a debilitating problem both within and outside the ICU. Significant short term consequences include difficulty in weaning off mechanical ventilation and increased risk of mortality (7). In some patients the effects of muscle wasting can persistent beyond hospital stay, resulting in functional impairment and the inability to carry out activities of daily living or return to work (5).

Critically ill adults experience elevated muscle protein breakdown (MPB) early in the disease course with a depression in muscle protein synthesis (MPS), resulting in a net negative muscle protein balance (6,8). MPS appears to increase with time while MPB remains constant, resulting in a less negative net protein balance (8). Although the exact pathophysiology is unclear, drivers of critical illness muscle wasting are likely multi-modal—an interaction between metabolic alterations and ICU therapy (9). Pro-inflammatory cytokines with sepsis (10), hyperglycemia (11), sedation and immobilization during mechanical ventilation (11), and high corticosteroid dose (11) are some factors that can trigger MPB and/or suppress MPS.

It is unclear whether children experience similar MPS and MPB changes as that in adults. Like adults, children are also exposed to the aforementioned insults during critical illness (12). Yet, children differ in metabolism and body composition (13), suggesting differences in skeletal muscle turnover than adults. Understanding protein turnover in pediatric critical illness is an important step in reducing or preventing muscle loss. The aim of this narrative review was to explore the evidence for muscle wasting in critically ill children through pathophysiology of muscle wasting and existing pediatric literature on muscle protein homeostasis. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tp-20-298).

Methods

Medline, Embase and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched from the earliest available dates up until June 2020. Keywords and major subject headings used in combination included: “skeletal muscle”; “muscle protein synthesis”, “muscle protein degradation”, “protein metabolism”; “growth and development”, “nutrition”, “immobility”, “exercise”, “disease”, “critical illness”. Results were limited to full articles and those pertaining to children (0–18 years). Conference abstracts and those pertaining to neuromuscular disease were excluded. After accounting for duplicates, titles abstracts were scanned and full articles were retrieved for shortlisted papers. Additional relevant studies were identified from hand-searching of reference lists of the shortlisted articles.

Muscle protein turnover

The process of muscle protein homeostasis, summarized in *Figure 1*, is well known and has been detailed elsewhere (14,15). Briefly, muscle growth or atrophy is determined by the net balance of MPS and MPB. When MPS exceeds MPB, there is a resultant net positive balance and muscle accretion occurs, whereas atrophy occurs when MPB exceeds MPS. MPS is energy dependent, controlled by various pathways which centers around the mammalian target of rapamycin (mTOR) and Protein Kinase B (Akt) (16). One of the major pathways for MPS is referred to as the Insulin-like Growth Factor 1/Phosphotidylionositol-3-kinase/Protein kinase B (IGF-1/PI3K/AKT) pathway, although anabolism can also occur via direct activation of mTOR by amino acids (15,17,18). Various upstream factors including IGF-1 and amino acids, activate Akt and mTOR, which in turn signal the three groups of proteins: Eukaryotic Initiation Factors (EIFs), Eukaryotic Elongation Factors (EEFs) and Eukaryotic Release Factors (ERFs) to carry out initiation, elongation and termination respectively (15).

MPB occurs mainly via the Ubiquitin Proteasome Pathway (UPP), and to a smaller extent the lysosomal and calpain proteolytic pathways (19,20). The UPP can be activated by phosphorylation of AKT, resulting in FOXO translocation to the nucleus upregulating ubiquitin ligases. Two ubiquitin ligases found responsible for increased UPP activity are the Muscle Ring Finger 1 (Murf-1) and the atrogin-1/F-box component (MAFbx). Of note, AKT independent activation can occur via NFκB, likely downstream of TNF superfamily receptors (21).

During critical illness, many factors upregulate MPB or inhibit MPS, or both. Risk factors associated

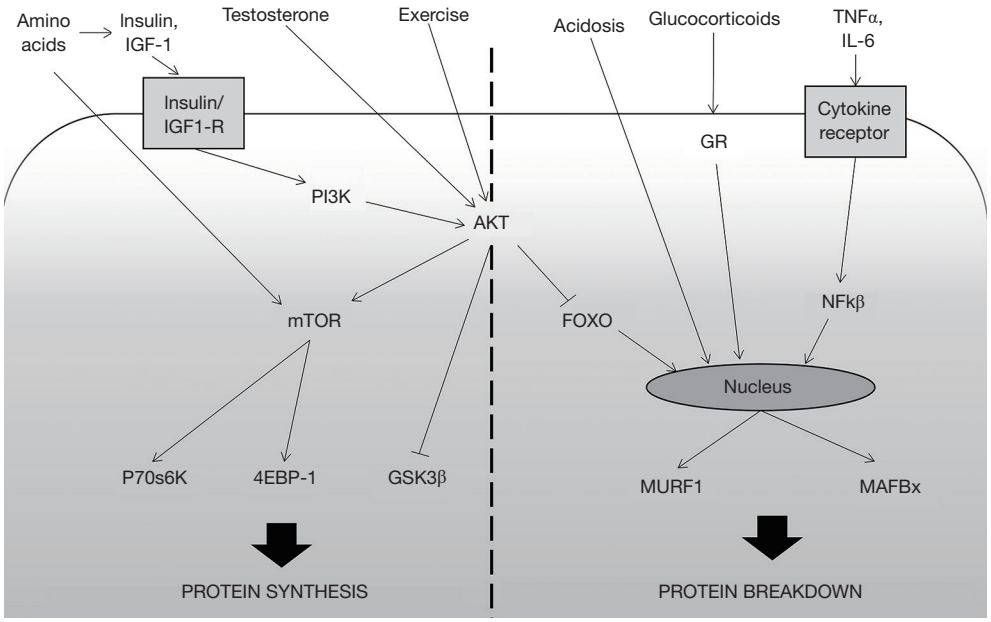

Figure 1 Simple depiction of muscle protein synthesis and breakdown pathways. On the left of the image are factors promoting muscle protein synthesis, on the right are factors promoting muscle protein breakdown (6). 4EBP-1, 4E binding protein 1; AKT, protein kinase B; FOXO, forkhead box O; GR, glucocorticoid receptor; GSK3β, glycogen synthase kinase 3 beta; IGF-1, insulin-like growth factor 1; IGF1-R, insulin-like growth factor receptor; IL-6, interleukin 6; MURF1, muscle ring finger 1; MAFBx, muscle atrophy F-box/atrogin-1; mTOR, mammalian target of rapamycin; NFκβ, nuclear factor kappa beta; PI3K, phophoinositide 3-kinase; p70s6K, p70 s6 kinase; TNFα, tumor necrosis factor alpha.

with ICU muscle wasting include sepsis (10,11), organ dysfunction (11), mechanical ventilation (11), acute lung injury (6), hyperglycemia (22) and high corticosteroid dose (11). Sepsis results in the release of pro-inflammatory cytokines and oxidizing free radicals, which have been shown to upregulate production of Murf-1 (23) and inhibit MPS via decreased phosphorylation of mTOR and downstream eukaryotic initiation factors (24). Patients are typically mechanically ventilated, sedated and immobilized, reducing the mechanical load on the muscle, which can in turn upregulate MPB and decrease MPS resulting in disuse atrophy (25). The mechanistic processes are described further in following sections. However, interventions focusing on appropriate sedation dose and duration, as well as early mobilization, have shown promising results to counter this (26,27). Hyperglycemia likely increases muscle breakdown via caspase proteolysis and UPP (28), while corticosteroid use has been associated with increased ubiquitin mRNA encoding and higher Murf-1 and MAFbx expression (29).

Direct measurements of MPS usually involve stable isotope infusions followed by skeletal muscle biopsy to determine the isotope incorporation rate (30). This is usually done in conjunction with measuring muscle protein balance across a limb via blood flow, and estimating limb MPB via tracer dilution (31). Molecular drivers of MPS and breakdown, e.g. mTOR, Murf-1 and MAFbx, have also been used to identify cellular pathways and mechanisms for muscle protein turnover (6,32), though no single protein currently serves as a good marker for protein turnover (6,33). Due to these limitation, isotope incorporation studies have mostly been conducted in animals (34,35), a major constraint in their generalizability.

As such, whole body protein turnover studies have been used to extrapolate muscle protein turnover (*Table 1*) (36). Nitrogen balance has been traditionally used to reflect whole body protein balance, but can be inaccurate due to methodological limitations and physiological instabilities (37). More recently, the accuracy has improved using stable isotope studies (37). However, the proportion of whole body protein turnover that is attributable to muscle varies depending on metabolic state, and thus whole body protein turnover may not be accurate reflection of MPS in critical illness (36,38). Nevertheless, together with

Table 1 Methods used to study muscle protein turnover

Method	Notes	Limitations
Stable isotope incorporation into muscle	Most common and robust method for studying muscle protein synthesis. Muscle breakdown usually inferred via tracer dilution	Invasive as muscle biopsy required
3-Methylhistidine (3MH)	Muscle breakdown inferred from 3MH, a breakdown product of myofibrillar proteins (myosin and actin)	3MH may not be specific to skeletal muscle
		Animal-free diet required throughout study
Nitrogen balance	Measures the difference between nitrogen (protein) intake and excretion	Difficult to collect accurate samples of nitrogen excretion
		Unable to distinguish between breakdown and synthesis rates
Whole body protein isotope turnover	Measures whole body isotope incorporation and excretion. More accurate than nitrogen balance, non-invasive as muscle biopsy not required	Whole body protein turnover may not reflect muscle protein turnover
Molecular signaling proteins	Signaling proteins involved with muscle breakdown or synthesis, including mTOR, MuRF1, MAFbx	Concentrations may not necessarily reflect rates of muscle protein synthesis or breakdown
		No single protein serves as a good marker for protein turnover

mTOR, mammalian target of rapamycin; MuRF1, muscle ring finger 1; MAFbx, atrogin-1/F-box component.

observations from healthy children and children with non-critical illness, these protein turnover studies provide some insight to possible mechanisms driving muscle turnover in critically ill children.

MPS and breakdown in healthy children

Growth in healthy well-fed infants is rapid, where MPS and MPB are highest (34,39). Isotope incorporation studies show that MPS rates in rats are highest at birth and fall to a third at weaning, then a further 5–6 times to reach adult levels (35,39). Decreasing MPS rates with age has been attributed to declining growth factors and resistance to anabolic agents (40). MPB is also high during rapid growth presumably to allow for muscle remodeling, decreasing at a slower rate than that of MPS from infancy to adulthood (39,41). The exception to this is during puberty, where whole body protein turnover using [1-^{13}C] leucine tracer showed significantly lower proteolysis in pubertal children compared to pre-pubertal children while whole body protein synthesis rates were similar or slightly decreased (42,43). Lower proteolysis may be explained by the higher concentrations of growth promoters (e.g., insulin, IGF1) in pubertal children (42,43). The net positive balance throughout childhood results in continuous muscle deposition, until MPB and MPS eventually reach an equilibrium after puberty, resulting in stable adult levels (39,44). During these stages, various factors can influence muscle protein turnover (*Table 2*).

Growth factors and hormones

Differences in muscle protein turnover during different stages of infancy, childhood and adolescence may be partially explained by growth factors including growth hormone (GH) and IGF-1. IGF-1 levels are low in infancy, rising steadily and peaking during puberty, decreasing after (91,92). GH levels follow a similar trend and are generally higher in pubertal children than in pre-pubertal children or adults (93). Their necessity for muscle growth is evident in that both IGF-1 and GH knockout mice have consistently retarded growth and reduced muscle mass (94). Such effect is also seen in children with GH and IGF-1deficiency (95), which improves after exogenous GH therapy (96).

IGF-1 stimulates MPS mainly through the IGF-1 receptor and activation of PI3K and AKT, which subsequently phosphorylates mTOR and GSK3B MPS pathways while inhibiting MPB (97,98). GH appears to

Table 2 Skeletal muscle protein synthesis and breakdown in response to various factors

	Child		Adult	
	MPS	MPB	MPS	MPB
Anabolic drivers				
GH/IGF1 (41,45,46)	↑[a]	↓[a]	↑[a]/↔[a]	↓[a]
Testosterone (47,48)	↑[a]	↔[a]	↑	↔
Insulin (49-54)	↑[a]	↓[a]	↑[a]/↔	↓[b]
Leucine (amino acids) (40,51,55-57)	↑↑[a]	↔[a]	↑[b]/↔[b]	↓[a]/↔[a]
Resistance exercise (58-60)	?	?	↑/↔	↑/↔
Aerobic exercise (41,61)	↑[a]	?	↑/↔[a]	↑[a]
Low dose glucocorticoid (62,63)	↔	↓	↔[a]	↓[a]
Catabolic drivers				
Starvation[c] (64-66)	↓↓[a]	↑[a]	↓[a]	↑[a]/↔[a]
Marginal malnutrition[d] (39)	↓[a]	↓[a]	↔[a]	↔[a]
Immobility (67-69)	↓[a]	↑[a]	↓	↑[a]/↔
Burn[e] (70-74)	↑↑	↑↑	↑	↑↑
Amino acids/protein (73-75)	↔	↔	?	?
Exercise (76)	?	?	?	?
IGF1/rGH (77,78)	↑	↔	↑	?
Oxandrolone/testosterone (79,80)	↑	↔	↔	↓
Beta blocking agents (81)	↑	↔	?	?
Sepsis[e] (82-84)	↓[a]	↑[a]	↓[a]	↑[a]
Leucine/amino acids (82,85,86)	↑[a]	?	↔[a]	↔[a]
Insulin/IGF1 (49,52,85)	↑[a]	?	↑[a]	↓[a]
Acidosis (87-89)	↓[a]	↑[a]	↓	↑
High dose glucocorticoid (47,90)	↓[a]	↑[a]	↓[a]	↑[a]
Critical illness (6)	?	?	↓	↑

↑, Increased; ↓, decreased; ↔, no change; ?, unclear or no evidence; GH, growth hormone; IGF1, insulin-like growth factor 1; rGH, recombinant growth hormone; MPS, muscle protein synthesis; MPB, muscle protein breakdown. Studies are human studies except as specified: [a], animal studies; [b], animal and human studies; [c], Starvation is defined as complete food deprivation; [d], marginal malnutrition is defined as an intake that may be sufficient for maintenance, but insufficient for growth; [e], Sub-points demonstrate effects that are in addition to that observed in the major factor.

act by stimulating IGF-1 mRNA expression, but also independently by increasing myotube size via cell fusion (96,99). The complete anabolic pathway of GH is unclear and still being studied (100).

GH and IGF-1 are also important for puberty, both in the onset of as well as growth during puberty (101,102). Higher IGF-1 concentrations were observed in pubertal children which corresponded with leucine retention, and may explain the lower proteolysis seen in pubertal children (42,43). GH and IGF-1 promotes protein synthesis while inhibiting fat deposition (101), promotes cartilage and bone formation for linear growth (101), and interacts with sex steroid hormones to amplify their action during puberty (103). In addition, sex steroid hormones are also an independent determinant

of muscle mass—male pubertal rats given testosterone have greater muscle growth; hypogonadal adolescent boys experience an increased muscle mass after testosterone administration (101,104). Testosterone appears to increase satellite cell numbers and muscle fiber size (105). In females, the opposite is seen as estrogen and progesterone appear to inhibit MPS in pubertal ovariectomized rats (106). Increased MPS may instead be due to the indirect action of estrogen stimulating GH production (44,107). Higher GH, IGF-1 and sex steroid hormones in males released during puberty are likely responsible for greater muscle deposition compared to females (102).

Adults may be less responsive to growth hormones and factors than in children. Provision of GH does not consistently activate MPS, particularly in the elderly (108,109). Although GH administration was able to increase MPS in young men, GH was unable to increase IGF-1, MPS rates, or muscle fiber size in elderly men (108,109).

Nutrition

Nutrition is crucial in maintaining muscle mass, demonstrated by animal feeding and starvation models (65,82). Feeding increases amino acid levels, thus stimulating MPS (49,110). This stimulatory effect appears to be primarily achieved by the branched-chain amino acid (BCAA) leucine, but not valine, isoleucine or non-BCAAs (56,111). However, leucine action is still dependent on total amino acid availability, as leucine supplementation alone could not stimulate MPS in starved piglets unless amino acids were infused concurrently (112).

Feeding also activates MPS and inhibits MPB via insulin release, which is best achieved with pulse feeding instead of a constant provision of nutrients, as shown by the inability for continuous feeding to stimulate insulin and amino acid increases in neonatal piglets (50,51). However, a recent trial in critically ill adults found that bolus feeding was not more protective against muscle wasting than continuous feeding (113). Conversely, insulin resistance inhibits MPS and lean body mass accretion as shown by dual-energy X-ray absorptiometry (DXA) (114).

The response to nutrition also appears to be age-dependent. Ten-day-old pigs exhibited higher post-prandial MPS rates than 28-day-old pigs (115), while some elderly rats and humans showed no evident change in MPS (40,57). These attenuations are hypothesized to be due to several factors, including decreased sensitivity to amino acids and lower insulin production with feeding (35,57), a drop in activation of insulin receptors in skeletal muscle (34), and decreased MPS signaling proteins with age (40). Similarly, starvation resulted in rapid inhibition of MPS and up-regulation of MPB in newborn and young animals, while less drastic changes were observed in adult animals (64-66). With marginal malnutrition, decreases in both MPB and MPS were evident in young, but not adult rats (39). Fortunately, these decreases in MPS were reversed after nutritional rehabilitation (39). Collectively, these emphasize the dependence of muscle homeostasis and growth on nutrition in the young.

Immobility and exercise

Immobility in adults results in downregulation of MPS without change in MPB (68,69), while in young rats both downregulation of MPS and upregulation of MPB occur (67). Unloading of hind limb in infant rats for 3 months resulted in a smaller soleus leg muscle fiber size than controls despite reloading, implying long-term deficits in muscle mass (116).

Resistance exercise improves MPS and muscle protein balance in adults (59,60). However, muscle hypertrophy is thought to occur only in the presence of androgens, which occurs in early and late adolescence (117). In pre-pubertal children, muscle strength improvements may result from neurological adaptations instead of muscle size changes. Pre-pubescent boys who underwent resistance training for 5 months experienced increases in strength independent of changes in muscle cross sectional area (118). Increases in upper-arm and mid-thigh strength were more closely correlated with improved motor skill coordination and motor unit activation (118). In contrast, rat models demonstrate that aerobic exercise appears to have a greater anabolic effect in the young (41).

Nutrition is also important in exercise associated protein homeostasis, as essential amino acids attenuated MPB and enhanced MPS after resistance exercise in adults (58). In children, whole body [^{15}N]glycine tracer protein turnover studies suggest similar effects as intake of protein or protein-containing food has been shown to improve protein balance in children after exercise (119).

Alterations of muscle protein homeostasis in disease states

Burns

In disease states, muscle turnover in children is altered

due to a variety of factors. Muscle protein turnover studies utilizing isotope incorporation with muscle biopsy in disease states are rare and mostly limited to children with burns. Several isotope tracer turnover studies using [ring-$^{13}C_6$]phenylalanine accompanied by vastus lateralis biopsy have been conducted in children with severe burn injuries (70,71,79). Burn injury results in a state of inflammation characterized by high inflammatory cytokine concentrations such as TNF-α and IL-6 (120), which can trigger MPB pathways via NFKB activation (121). Phenylalanine tracer studies demonstrate increased muscle breakdown in the leg immediately post burn (1–2 weeks), which continues to increase and peak at 4 weeks post burn before falling to approach normal levels after 2 years (70,71). MPS follows a similar pattern (70,71), and the net muscle protein balance depends on several factors including burn size and degree, sepsis, time to excisional treatment, age and gender (70,122). Muscle wasting and loss of lean body mass can continue up to even after 9 months post injury (123). Similar hypermetabolic responses have been reported in adults with burn injury (124).

Therapies to reduce catabolism in burned children include nutrition, exercise therapy, anabolic agents and beta blocking agents (76,79,81,125). Although supplemental whey protein improved weight gain and plasma amino acid levels in children 1.5 months after major burn (125), [13C6] phenylalanine incorporation studies show that immediately post-burn, high dietary protein in children increased protein synthesis of the skin but not muscle, suggesting a prioritization of wound healing over preservation of muscle (74). Similarly, provision of intravenous amino acids were unable to significantly increase MPS across the leg 6 months post-burn (73,75), although this was possibly due to small sample sizes.

A combination of resistance and aerobic exercise for 12-weeks significantly improved muscle strength and lean body mass gain in burned children as shown by DXA (76). However, whether this was due to an attenuation of MPB or increased MPS is unclear. MPS rates by [ring-$^2H_5$] phenylalanine isotope incorporation were not significantly higher than in controls, although this could be because MPS was not measured immediately but at ≥48 hours post-exercise (76).

Exogenous anabolic agents appear to ameliorate catabolism in children with burns by modulating MPS. Short-term provision of IGF1 and beta-blockers following major burns were able to stimulate MPS (77,81), while recombinant human GH increased lean body mass (126,127). Oxandrolone administered soon after burn injury also increased MPS and net muscle protein balance (79), the anabolic effect being greater when combined with aerobic and resistance exercise (123). Provision of oxandrolone for a year post-burn continued to aid lean body mass accrual for up to 5 years as shown on DXA scans, although this only occurred in children above 7 years, possibly as they were less anabolic than younger children (123,128,129).

Sepsis, glucocorticoids and acidosis

Dysregulations in the GH/IGF-1 axis have been observed in critically ill patients. In a cohort of children with sepsis or trauma, levels of IGF-1 were lower and levels of GH were higher than those in healthy children (130). The increased GH was thought to be a response to the increase in inflammatory cytokines produced during critical illness, as well as a lack of feedback inhibition from the depressed IGF-1 levels, creating a state of GH resistance. In another cohort of critically ill children with sepsis, study authors found that GH concentrations were higher and IGF-1 concentrations were lower in non-survivors compared to survivors, suggesting that this dysregulation was predictive of mortality (131). However, it is unclear how this dysregulation translates to protein turnover in critically ill children.

Age-different responses have also been observed in sepsis-induced animal models (83). Sepsis has been shown to decrease MPS due to reduced mRNA translation of anabolic signaling (132), while MPB remains high through upregulation of ubiquitin ligases MuRF1 and MAFbx (121). The increase in MuRF1 and MAFbx during sepsis is greater in older than young animals (83). In response to feeding, MPS is increased in septic neonatal (131) but not adult animals (83), further suggesting that the young may be more sensitive to stimulants of MPS than adults.

The role of glucocorticoids in pediatric muscle protein turnover appears equivocal, and possibly dependent on dose and the condition in which muscle wasting occurs (133). Glucocorticoids are thought to independently increase MPB by upregulating expression of FOXO, MuRF1 and MAFbx (134), as well as reducing MPS through inhibiting amino acid and IGF-1 production, and suppressing mTOR signaling (135,136). Glucocorticoids also appear to be necessary for sepsis and tumor induced MPB, as Murf-1 and MAFbx mRNA levels are not significantly increased in young animal models where glucocorticoid receptors were blocked or knocked-out (121,137). High dose steroids

upregulated MPB and downregulated MPS in young rats (90), and have been associated with increased protein breakdown and decreased synthesis in children with Crohn's disease (138). High dose steroid use has also been associated with myopathy in pediatric asthma (139). However, low dose glucocorticoids prevented muscle atrophy through suppression of Akt/FOXO inhibition and blunting of lysosomal protein breakdown in adult rats (63). Low-dose glucocorticoids have also been shown to decrease MPB (without change in MPS), with accompanying increases in muscle mass and strength in boys with Duchenne muscular dystrophy (62).

The presence of acidosis has also been shown to affect protein homeostasis in children with chronic renal failure (140). Whole body protein turnover studies in children with chronic kidney disease (CKD) demonstrate breakdown increased with the severity of acidosis, while whole body protein synthesis was comparable (140). Although whole body protein turnover is not necessarily reflective of muscle protein turnover, metabolic acidosis has shown to increase MPB in adults with CKD (87). Muscle mass visualized by peripheral quantitative computed tomography and DEXA have also been found to be reduced in CKD children (5–21 years) compared to healthy children, with muscle deficits that correlated with the severity of CKD (141,142).

Further research needed for clinical translation

Critically ill children, like adults, are exposed to many risk factors for muscle wasting [e.g., sepsis (12), hyperglycemia (143), malnutrition (144) and high dose, prolonged corticosteroid use (145)]. Factors upregulating MPB, such as starvation, immobility and burns, appear to impact the young more than adults. The young are also more dependent on growth factors for muscle maintenance and growth than adults, suggesting that children may be more susceptible to muscle wasting than adults in the presence of critical illness-related starvation and immobility, especially during periods of rapid growth (i.e., infancy and puberty). Yet, children have proportionally fewer type 2 muscle fibers (146), which may be preferentially targeted in ICU muscle wasting (9), possibly resulting in less muscle wasting. The young also appear to be more responsive to anabolic agents and resilient to catabolism during sepsis and burns (34,72). Yet, whole body turnover studies have not demonstrated consistent evidence of improved protein balance with increased protein provision in critically ill children, possibly affected by other factors regulating protein turnover such as degree of inflammation (147,148). Unfortunately, without actual studies on muscle protein turnover, it is difficult to conclude the effect critical illness has on muscle in children.

In addition, of greater clinical relevance would be the effect of muscle wasting on health and outcomes of pediatric critical care survivors, and whether muscle wasting results in persistent impairment in function and strength as observed in adults (5). Muscle wasting due to major burns can result in loss of strength, power and aerobic capacity in children (76). Prolonged muscle loss can also reduce bone mineral content and limit growth potential through lowered mechanical load that the bone is exposed to (149), as observed in children with CKD (142). Pediatric intensivists are increasingly aware of morbidities following critical illness and are beginning to study the effect of critical illness on long-term outcomes (150). Physical limitations have been reported in survivors of critical illness (150), and body composition at PICU admission has been associated with functional impairment at discharge (151), but whether functional impairment is associated with muscle wasting in critically ill children has yet to be determined.

The limited evidence of muscle wasting in critically ill children is largely due to the methods currently available in studying muscle protein turnover. Less invasive and complex methods of identifying muscle wasting would be beneficial. Generalized weight loss and reduced mid upper arm circumference have been commonly reported in critically ill children. Losses in weight and mid-upper arm circumference correlated with lower energy and protein intakes, and were more evident in older than younger children, similar to children with burns (12,72,144). However, weight and arm circumference losses may be influenced by edema or fat loss (144), and methods to assess skeletal muscle would help better inform muscle-specific changes. Some methods used in adult ICUs include muscle mass visualization by ultrasonography, bioelectrical impedance analysis and tests of strength and physical function (hand grip strength, six-minute walk test) (5-7). A longitudinal study demonstrated loss in ultrasound-derived diaphragm and limb muscles thickness in critically ill children, which was greater in older children compared to younger children (152). Ultrasound, bioelectrical impedance analysis and strength and function testing are relatively simple and inexpensive tests that have just begun to be used in critically ill children (152-154), but demonstration of their validity in this population is needed. Research on muscle protein turnover has traditionally been restricted

by the need for muscle tissue biopsies, which are invasive and thus difficult to obtain, especially in children. However, recent work in cancer cachexia patients seem to suggest the feasibility of using urine and serum for metabolomics research to understand the mechanistic pathways of muscle wasting (155,156), which could potentially be translated to critical illness. Future studies using these methodologies and associating them with functional outcomes would further characterize the clinical significance of muscle changes in these children.

Limitations

Extrapolation of muscle protein homeostasis from animals and other pediatric populations to critically ill children may be too simplistic given differences in metabolism (157). Detailed consideration of factors such as dose and time-course of interventions across populations is needed. Furthermore, given the heterogeneity of critical illness, metabolic responses may vary depending on primary diagnosis, co-morbidities and illness severity. Generalizations from a specific patient group (e.g., burns) to the entire pediatric ICU cohort may be erroneous, and speculations of muscle wasting patterns may have to be tailored according to the risk factors observed in individual patients. Finally, we did not delve into the role of microRNAs or satellite cells as these were beyond the scope of this review, although their role in muscle homeostasis has been studied increasingly in recent years (14).

Conclusions

Factors influencing muscle protein turnover appear to be similar in adults and children, but baseline protein homeostasis and response to catabolic and anabolic stimuli may be different. Compared to adults, children are equally or more susceptible to muscle catabolism with starvation, burn injury and immobility. However, children, particularly young ones, appear to be more responsive to anabolic factors. Critically ill children experience muscle wasting, which may be reversible with the right anabolic interventions. Closer study of muscle protein turnover at various ages, time points of critical illness and response to therapies are needed in critically ill children.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Pediatrics* for the series "Pediatric Critical Care". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/tp-20-298

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-298). The series "Pediatric Critical Care" was commissioned by the editorial office without any funding or sponsorship. JHL served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Translational Pediatrics* from Nov 2019 to Nov 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Ong C, Lee JH, Leow MKS, Puthucheary ZA. A narrative review of skeletal muscle atrophy in critically ill children: pathogenesis and chronic sequelae. Transl Pediatr 2021;10(10):2763-2777. doi: 10.21037/tp-20-298

