



Nutritional Rehabilitation After Prolonged Critical Illness: The Year After the Intensive Care Unit

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Abstract

Muscle loss during critical illness is rapid, large and well characterised. In 63 patients studied prospectively from admission, rectus femoris cross-sectional area fell 17.7 per cent by day 10, and in the subset examined by all three methods the ratio of protein to DNA fell 29.5 per cent by day 7. Loss was concentrated in those with multiorgan failure, 15.7 per cent by day 7 against 3.0 per cent with single organ failure. The inference that more protein should therefore be given has been tested. In 1,301 mechanically ventilated patients randomised to at least 2.2 g/kg per day or no more than 1.2, time to discharge alive gave a hazard ratio of 0.91 (95% CI 0.77 to 1.07) and 60-day mortality a risk ratio of 1.08 (0.92 to 1.26). Among those with acute kidney injury the higher dose was associated with slower discharge, hazard ratio 0.50 (0.40 to 0.80), and higher mortality, 1.40 (1.10 to 1.80). A Bayesian re-analysis put the probability of harm on the primary outcome at 92 per cent. The year after the unit, which is where recovery actually happens, has almost no trial evidence at all.

Keywords: Critical illness; Muscle wasting; Protein delivery; Rehabilitation; Post-intensive care

Introduction

Survivors of prolonged critical illness leave the intensive care unit weak, and many remain so a year later [1,2,3]. Physical function, employment and quality of life are affected well beyond hospital discharge, and the syndrome has a name and a literature [2,3,4].

Nutrition is an obvious candidate for intervention because the tissue lost is protein and because intake is measurable and modifiable [5,6]. The reasoning is intuitive: muscle disappears, so supply the substrate to rebuild it [6,7].

This review examines that reasoning against the evidence, and asks where in the year after the unit the evidence actually is.

Objective

This review sets out to establish four things from the published literature. First, what is known about the magnitude and timing of muscle loss in critical illness. Second, what happened when higher protein delivery was tested in a randomised trial. Third, how that result should be read. And fourth, what evidence exists for the period after hospital discharge, which is the subject of this article.

Literature Review

What is lost, and how fast: A prospective study recruited 63 critically ill patients within 24 hours of admission, 59 per cent male, mean age 54.7 years (95% CI 50.0 to 59.6), with a mean APACHE II score of 23.5 (21.9 to 25.2) [8]. Rectus femoris cross-sectional area fell 17.7 per cent by day 10 (95% CI 25.9 lower to 8.1, $P < .001$). In the 28 patients assessed by all three methods, cross-sectional area fell 10.3 per cent by day 7, fibre cross-sectional area 17.5 per cent, and the ratio of protein to DNA 29.5 per cent [8]. Myofibre necrosis was present in 20 of 37 patients, 54.1 per cent [8].

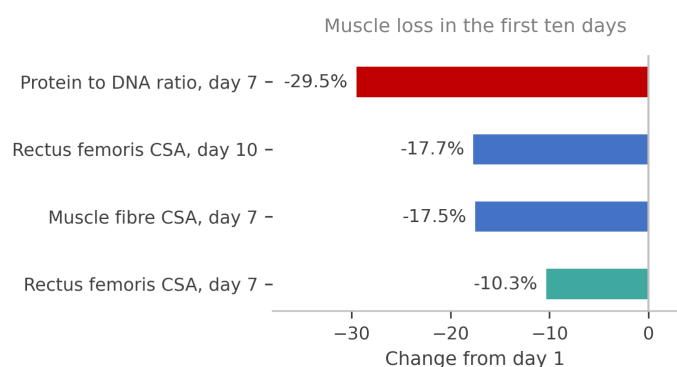


Figure 1: Muscle measures over the first ten days of critical illness [8]

Severity determines the rate: By day 7, loss was 15.7 per cent in patients with multiorgan failure against 3.0 per cent with single organ failure ($P < .001$), and the separation was already present at day 3 at 8.7 against 1.8 per cent ($P = .03$) [8]. These organ-failure intervals are those of the published erratum rather than the original article [8,9]. The pattern indicates that wasting tracks the severity of the illness rather than the duration of fasting, which is the first difficulty for a purely nutritional account [8,10].

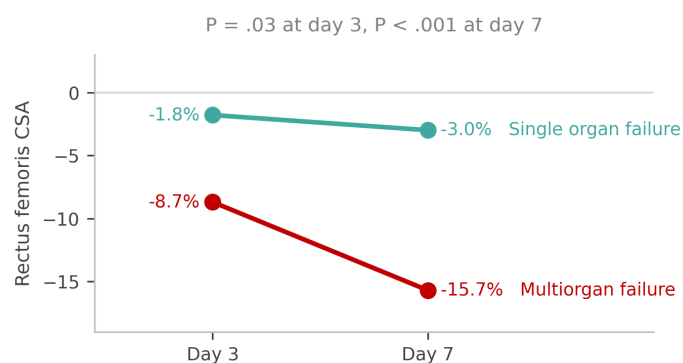


Figure 2: Rate of loss by organ failure status [8,9]

Measure	Change	Interval
Rectus femoris CSA, day 7	-10.3%	6.1 to 14.5 [8]
Rectus femoris CSA, day 10	-17.7%	25.9 lower to 8.1 [8]
Muscle fibre CSA, day 7	-17.5%	5.8 to 29.3 [8]
Protein to DNA ratio, day 7	-29.5%	13.4 to 45.6 [8]
Myofibre necrosis	20 of 37	54.1% [8]

Table 1: Muscle measures as published, with the erratum applied [8,9]

The intervention was tested: A pragmatic registry-based randomised trial across 85 centres enrolled 1,329 mechanically ventilated patients at high nutritional risk between January 2018 and December 2021, analysing 1,301, with 645 assigned to at least 2.2 g/kg per day of protein and 656 to no more than 1.2 g/kg per day for up to 28 days [11]. Time to discharge alive from hospital up to 60 days gave a hazard ratio of 0.91 (95% CI 0.77 to 1.07, $p = 0.27$) and 60-day mortality a risk ratio of 1.08 (0.92 to 1.26) [11,12].

The honest complication: The trial's own conclusion was that higher doses did not improve time to discharge alive and might have worsened outcomes in patients with acute kidney injury and high organ failure scores [11]. A post hoc analysis in those with acute kidney injury found the higher dose associated with slower discharge alive, hazard ratio 0.50 (0.40 to 0.80, $p = 0.001$), and higher 60-day mortality, risk ratio 1.40 (1.10 to 1.80) [13]. No subgroup suggested benefit [13].

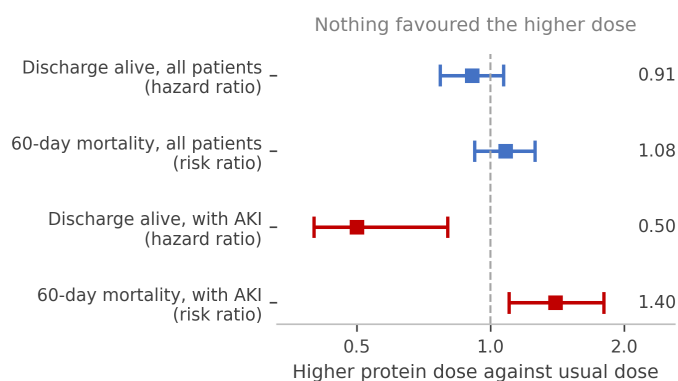


Figure 3: Higher against usual protein dose, overall and in acute kidney injury [11,13]

A second reading of the same data: A Bayesian re-analysis using weakly informative priors reported a hazard ratio for time to discharge alive of 0.91 (95% credible interval 0.80 to 1.04) with a 92 per cent probability of harm from the higher dose, and probabilities of 97 and 95 per cent for interactions with baseline creatinine and organ failure score respectively [14]. The frequentist and Bayesian analyses agree on the point estimate and differ in what they permit to be said about it; neither supports the intervention [11,14].

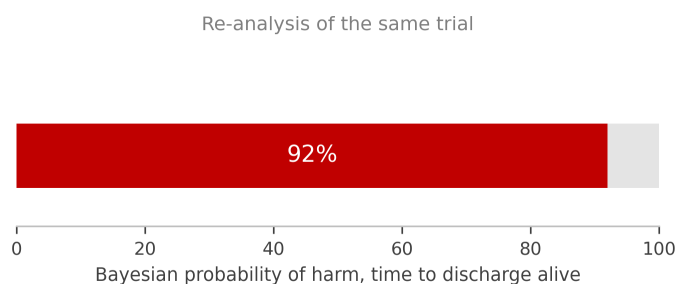


Figure 4: Probability of harm on the primary outcome in the re-analysis [14]

Analysis	Result
Primary, discharge alive	HR 0.91 (0.77-1.07) [11]
Primary, 60-day mortality	RR 1.08 (0.92-1.26) [11]
Acute kidney injury, discharge	HR 0.50 (0.40-0.80) [13]
Acute kidney injury, mortality	RR 1.40 (1.10-1.80) [13]
Bayesian, probability of harm	92% [14]

Table 2: The trial and its re-analyses [11,13,14]

Why substrate alone does not rebuild muscle: During critical illness muscle protein synthesis is depressed relative to breakdown and does not respond normally to amino acid provision, a state described as anabolic resistance [8,10,15]. The original prospective study measured synthesis and breakdown directly and found the imbalance present from the earliest days [8]. Inflammation, immobility, sedation and organ failure all contribute, and none is corrected by increasing supply [10,15,16]. The failure of the trial is therefore consistent with the physiology rather than surprising against it (Figure 6) [8,10,15].

The step that fails

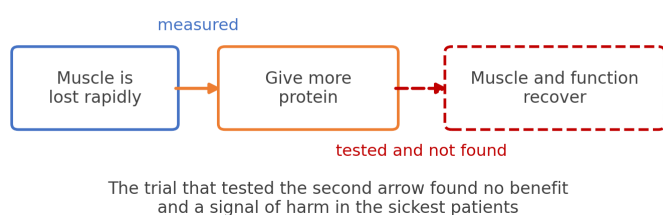


Figure 6: The step in the reasoning that the trial tested [8,11]

Where the evidence stops: The trials that exist concern the period in the unit. Intake after transfer to the ward is consistently reported as falling short of estimated requirements, and intake after hospital discharge is documented in small observational studies [17,18,19]. Randomised evidence for nutritional intervention during the months at home, which is the period this article is named for, is close to absent (Figure 5) [19,20,21]. The most studied phase is the one in which the intervention has been shown not to work, and the least studied is the one in which recovery occurs [11,19,21].

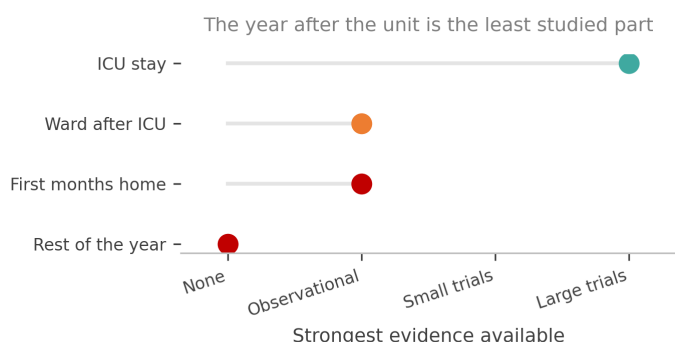


Figure 5: Evidence available by phase of recovery [11,17,19,21]

Why the later period might behave differently: Anabolic resistance is a feature of acute illness and inflammation, and both resolve, so the physiological argument against supplementation during the unit stay does not automatically extend to the convalescent period [15,16,22]. Combining nutrition with exercise is the approach that works in other populations losing muscle, and the trials of rehabilitation after critical illness have generally tested exercise without a nutritional component [20,22,23]. This is a plausible gap rather than a demonstrated opportunity [21,22,23].

What rehabilitation trials have found: Structured physical rehabilitation after critical illness has been examined in multiple randomised trials with heterogeneous interventions, timing and outcomes, and syntheses report inconsistent effects on physical function and quality of life [20,23,24]. Where nutrition has been included it has usually been a co-intervention rather than a randomised factor, so its contribution cannot be separated [21,23]. The design that would answer the question, randomising nutritional support within a rehabilitation programme after discharge, has been proposed more often than conducted [21,22,24].

Question	Status
Is muscle lost rapidly in the ICU?	Established [8]
Does severity drive the loss?	Established [8]
Does more protein in the ICU help?	No, possible harm [11,13,14]
Is intake low after the ICU?	Reported, observational [17,18]
Does support after discharge help?	Not tested [19,21]

Table 3: Five questions and the evidence available for each

Measuring the right outcome: Trials in this field have used mortality and length of stay, which are insensitive to what survivors care about, and long-term physical function and patient-reported quality of life have been identified as the outcomes that matter after critical illness [12,25,26]. A trial powered for discharge alive can miss an effect on function at six months, and none of the completed protein trials was designed to detect one [11,12,25]. That is a reason for caution in both directions rather than an argument that benefit exists [11,25].

Who the patients are: Survivors of prolonged critical illness are heterogeneous in age, premorbid function and reason for admission, and pooled estimates conceal that [1,3,26]. Those with prolonged multiorgan failure lose the most muscle and are also the group in whom the higher protein dose signalled harm, which means the patients with the greatest apparent need are those for whom the evidence is least reassuring [8,11,13]. This is uncomfortable and it is what the data show [11,13].

The wider feeding trials point the same way: Large randomised trials of nutrition in critical illness have repeatedly failed to show benefit from delivering more. Early parenteral supplementation to reach targets produced slower recovery than tolerating a

deficit; energy-dense enteral formula did not change 90-day mortality; and permissive underfeeding was not inferior to standard feeding [30,31,32]. The protein trial is therefore not an isolated negative result but the most recent member of a consistent series [11,30,31,32]. Any account of the field that treats it as anomalous is misreading the pattern [11,32].

Achieved delivery is narrower than assigned: Trials in this field routinely achieve less separation between arms than their protocols specify, which attenuates any true effect and complicates interpretation of a null result [11,33]. In the protein trial the achieved high-dose delivery fell short of the assigned target, so the comparison made was narrower than the comparison designed [11,33]. This is a reason to hold the null result with some caution, and it does not explain the direction of the harm signal in the acute kidney injury subgroup [11,13,33].

Mobilisation is the other half: Early mobilisation during critical illness has been evaluated in randomised trials and is the intervention most plausibly paired with nutrition, since substrate without loading has no obvious anabolic stimulus [27,29,15]. Ultrasound methods used to track muscle in these studies have known reliability limits and measure a single site, which constrains what can be concluded about whole-body protein [28,29]. Both points bear on how a future combined trial should be measured rather than on whether it should be done [22,28,29].

Method

This is a narrative review of published literature. Sources were assembled by searching the indexed literature for prospective studies of muscle wasting in critical illness, randomised trials of nutritional delivery in and after intensive care, rehabilitation trials in survivors, and observational studies of intake after discharge [8,11,19].

Effect estimates are reproduced as their authors published them, with the interval attached. Where a published erratum has revised a value, the corrected value is used and the erratum noted [8,9].

No new patient data were collected and no search protocol was registered, so this is not a systematic review. Protein doses are described as the targets the trials assigned and are not recommendations for any individual patient.

Concluding Remarks

Muscle loss during critical illness is severe, rapid and driven by the severity of the illness rather than by the adequacy of intake. That much is established as clearly as anything in this field.

The response that follows intuitively from it has been tested and did not work. Higher protein delivery did not shorten time to discharge alive, did not reduce mortality, and in patients with acute kidney injury was associated with worse outcomes on both. A re-analysis of the same trial put the probability of harm

at 92 per cent. Whatever limits recovery in the acute phase, substrate supply is not it.

The year after the unit remains the least studied part of the illness and the part where recovery actually happens. Anabolic resistance resolves, exercise becomes possible, and the physiological objection that explains the ICU result does not obviously apply. That makes the convalescent period the reasonable place to look, and it is not where the trials have been done.

The deficit accumulates before anyone is discharged: Reported intake on the ward after transfer from the unit falls consistently short of estimated requirements, with interruptions for procedures, swallowing difficulty after prolonged intubation, and loss of the automatic delivery that tube feeding provided [17,18]. The transition out of the unit therefore removes the mechanism that was meeting requirements without removing the requirement, and it does so at the point when the anabolic resistance that made delivery futile is beginning to resolve [15,17,18]. If there is a moment when supply plausibly becomes limiting, this is it, and it falls between the two literatures [11,17,19].

Timing may be the variable that matters: Read together, the acute trials and the physiology suggest that the same intervention could be futile at one point in the illness and useful at another, which is a hypothesis about timing rather than about dose [10,15,22]. Trials to date have varied dose within a fixed early window rather than varying the window [11,30,31]. That the field has answered the dose question several times and the timing question not at all is a feature of how the trials were designed, not of what is clinically uncertain [11,22,32].

Study Limitations

The muscle wasting evidence rests principally on one detailed prospective cohort of 63 patients, and ultrasound measures of a single muscle group are an imperfect proxy for whole-body protein loss. The protein trial was pragmatic and unblinded to clinicians, and achieved separation between arms was narrower than the assigned targets.

Evidence for the post-discharge period is largely observational and drawn from small cohorts, so statements here about the absence of benefit in that period reflect the absence of trials rather than negative results. Findings from the acute phase should not be transferred to it in either direction.

What survivors say they want: Qualitative work with survivors identifies regaining independence, returning to work and being able to manage ordinary physical tasks as the priorities, rather than the intermediate measures the trials report [25,34]. Appetite loss, altered taste and early satiety are described as persistent and distressing well after discharge, and they are rarely captured as outcomes [19,34]. A research programme built around what survivors describe would look different from the one that exists

[25,26,34].

Practical implications while the evidence is absent: Nothing here argues for withholding nutritional care from survivors, and undernutrition after discharge remains a condition worth identifying and treating on its own terms [5,19]. What the evidence does not support is a claim that increasing intake accelerates recovery of muscle or function, and offering that expectation to a patient sets up a disappointment the data predict [11,19,21]. Describing the intervention as maintaining adequacy rather than driving recovery is both more accurate and easier to sustain [5,19,21].

What a trial would need to look like: It would recruit after hospital discharge rather than in the unit, randomise a nutritional component within a rehabilitation programme so the exercise stimulus is present in both arms, and measure physical function and patient-reported outcomes at six and twelve months [22,24,25]. Sample size would be driven by function rather than mortality, and retention would be the principal operational risk in a population with high ongoing morbidity [24,26]. None of these requirements is unusual; the trial has simply not been prioritised [21,24].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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