Does body mass index impact on muscle wasting and recovery following critical illness? A pilot feasibility observational study

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Key words

Obesity; Nutrition Support; Muscle wasting; Intensive care acquired weakness; Critical illness; Intensive Care.

Authors' contributions

ES conceived and designed the study, conducted the study, performed the statistical analysis and prepared the manuscript. LW assisted with data acquisition. MH, MS and LW informed the study design, provided supervision, and critically revised the manuscript for publication. MT assisted with statistical analysis and manuscript revision. All approved the final version.

Abstract

Introduction: Critical illness is associated with muscle loss, weakness and poor recovery. The impact illness and ensuing metabolic response has on obese patients is not known. Objectives were to test if obese patients lose less muscle depth compared to non-obese; if a reduction in muscle depth was associated with reduced strength and recovery; and to assess the feasibility of these methods with a range of Body Mass Index's (BMI).

Methods: Prospective observational pilot study of muscle depth in critically ill patients categorised by BMI. Muscle depth changes were assessed by ultrasound on study days 1, 3, 5, 7, 12 and 14. Strength was measured via handgrip dynamometry and Medical Research Council (MRC) sum score at waking and Intensive Care Unit (ICU) discharge. Level of dependency was measured with the Barthel index.

Results: 44 critically ill patients - 17 with normal BMI, 10 were overweight and 17 were obese. The 3 groups did not differ in baseline characteristics, except obese patients had significantly greater initial muscle depth. Muscle depth loss was similar between the BMI groups at each of the time points. Handgrip and MRC sum score were only possible in a small number of patients due to reduced alertness and weakness. The majority were deemed fully dependent based on the Barthel index.

Conclusions: Obese patients lost muscle depth in a comparable manner to non-obese patients, suggesting BMI may not prevent muscle depth loss. It was not possible to determine the effect on strength since clinical patient clinical condition precluded reliable measurements.

Introduction

Critical illness is associated with hypermetabolism and catabolism which results in a dramatic loss of muscle mass [1; 2]. Patients who are mechanically ventilated for longer than seven days frequently experience muscle wasting syndromes or profound weakness (referred to as intensive care unit (ICU) acquired weakness) [3; 4]. This is unequivocally associated with decreased survival, increased rates of infections, longer hospital stays and delayed recovery, and increase healthcare costs [5; 6].

While many different, potentially interacting pathophysiological mechanisms have been proposed for ICU acquired weakness [7] no previous work explored the possible role of patients body composition or body mass index (BMI). The prevalence of obesity is increasing in ICU with large retrospective databases suggesting prevalence rates of 26-31% [8; 9].

There is a lack of research detailing the nutritional and metabolic processes seen in obese critically ill patients. It is not clear what impact critical illness and the ensuing metabolic response has on obese patients and how this compares to non-obese patients. For example, patients with obesity maybe able to metabolise their excess adipose stores as the dominant fuel source and preserve muscle mass [10; 11; 12]. One study of only 17 patients (7 obese) investigated if the metabolic response to trauma is different between obese and non-obese critically ill patients. Obese patients experienced increased nitrogen losses and reduced protein synthesis compared to the non-obese patients [13], suggesting that critically ill obese patients may lose the ability to conserve protein stores.

Our study objectives were to: 1) test if obese patients lose less muscle depth compared to non-obese; 2) detect if a reduction in muscle depth was associated with reduced muscle strength and delayed functional recovery; and 3) as a pilot study, to assess the feasibility of performing these methods in patients with a range of BMI's in order to inform a larger trial.

Materials and methods

Study design

This was a pilot feasibility, prospective observational study of critically ill patients over a one -year period (2010-2011). Patients were recruited from the general ICU's in three tertiary UK teaching hospitals**.** Ethical approval was gained from the North West London Research Ethics Committee (NRES reference: 10/H0722/40). Written informed consent was obtained from patients or agreement sought from their designated representative, with retrospective patient consent obtained when full mental capacity was re-gained.

Inclusion criteria were: older than 18 years, BMI more than 19kg/m ^{2}, expected to be mechanically ventilated for longer than 48 hours, and being artificially fed. Pregnant patients were excluded.

Patients were entered into the trial within 72 hours of ICU admission. Baseline demographics included admission reason / diagnosis, number of comorbidities [(14)], severity of illness defined by Acute Physiology And Chronic Health Evaluation score (APACHE II), and anthropometric measurements (weight, height and BMI). Data on mortality, ICU length of stay and days on mechanical ventilation were collected on conclusion of the study.

Muscle depth

Peripheral muscle depth changes at three sites (bicep, forearm and thigh) were assessed by ultrasound in every participant on study days 1, 3, 5, 7, 12 and 14 to detect muscle depth change over time according to protocols described previously [(15; 16; 17)]. Three measurements were performed at each site and the mean calculated [(16)]. For each patient, all measurements were performed by the same investigator. Standardised training protocols were followed.

Physical Assessment:

Two measures of strength were used: hand grip strength and the Medical Research Council (MRC) sum score for muscle power [(3)]. These were measured at waking (sedation off and patient alert) and ICU discharge. To assess if the patient was awake enough to participate, a

four battery test was undertaken asking the following: open your eyes, follow my finger, stick your tongue out, and squeeze my hand.

The MRC sum score was carried out on six different bilateral muscle groups: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion. Strength in each muscle group was scored according to the six-point MRC system, in which a score of 0 was no contraction, 1 was a flicker of contraction, 2 was active movement with gravity eliminated, 3 was active movement against gravity, 4 was active movement against gravity and resistance and 5 was normal power. The maximum score is 60. A score below 48 was used as a cut off to indicate ICU acquired weakness or muscle wasting [18]. Two investigators (ES and LW) performed the MRC assessment after training from an experienced physiotherapist.

Handgrip strength was measured to detect changes in lower arm and hand strength of the dominant hand using a hydraulic handgrip dynamometer (JAMAR, Lafayette Instruments Lafayette, USA). The patient was positioned in a sitting position with elbow flexion of 90 degrees. An average of the three readings was used. A strength value below 11kg in males and 7kg in females corresponds with ICU acquired weakness or muscle wasting [19].

The Barthel index was undertaken to assess the ability to undertake activities of daily living. It measures the capacity to perform ten basic activities and gives a quantitative estimate of the patient's level of dependency and range from 0 (totally dependent) to 100 (totally independent). It has been used to assess functional recovery following critical illness [20; 21].

Nutritional intake

Patients were fed according to the units' feeding protocol which stated that the enteral route should be the first choice, and nutrition should be commenced within 48 hours of admission. If enteral nutrition failed or was contraindicated, parenteral nutrition was commenced. The treating dietitian set the energy and protein targets. Energy requirements were calculated using Schofield equation adding factors for stress and activity to make it clinically relevant [22] or the Penn State Equations [23; 24] (currently recommended as the most accurate way to predict energy requirements for both obese and non-obese critically ill

patients) [25; 26]. We had no access to indirect calorimetry. Protein requirements were calculated as 1.2-1.3g/kg actual body weight for normal weight patients [27; 28], 0.8-1.2g/kg actual body weight for obese [27] and adjusted to reflect clinical parameters such as renal and liver impairment, filtration and excess losses. Nutritional intake data were collected on a daily basis for the days that the patient remained in the study. For the analysis, the energy and protein prescription and received are expressed as Kcal/kg and gram/kg, respectively. This is the overall intake divided by body weight. This allows for direct comparison with other studies.

Anthropometric measurements

BMI was calculated using the most recent accurate body weight and height obtained from the patient's medical notes. If unavailable, the patient was either weighed or estimated on the ICU bed, or weights sought from family members. When height was not available it was estimated from ulnar length measurement, taken between the point of the acromion and the ulnar styloid. This value was then converted into an estimated height [29]

Statistical analysis

Descriptive statistics are presented as median and inter-quartile range, or mean and standard deviation. Patients were categorised into three independent groups according to BMI:

- Group 1 (Normal weight) BMI 19-24.9kg/m^2
- Group 2 (Overweight) BMI 25-29.9kg/m^2
- Group 3 (Obese) BMI ≥ 30kg/m^2

Comparisons between these groups were made using t-tests or Mann Whitney tests. Missing data was assumed to be missing at random. Missing day 7 values for the primary outcome were imputed by carrying forward day 5 values.

Regression analysis was undertaken to quantify the association between muscle loss (loss as % from initial at day 7) and the following variables; baseline BMI, age, gender,

comorbidities, APACHE II and thickest muscle depth. Results are presented as coefficients, p-value and 95% confidence intervals. All statistical analyses were performed using Stata 13 (Statcorp LP, USA). The statistical significance was defined at the 5% level.

Results

Baseline characteristics are shown in Table 1. Figure 1 presents the patient flow diagram. Thirty-three (75%) patients were male, median age was 58 years and admission APACHE II score was 20. There were no differences in baseline characteristics on admission. Six (14%) patients were recruited within 24 hours of admission, 50% (22/44) within 48 hours and 36% (16/44) within 72 hours of admission to ICU.

There was considerable loss to follow up observed in all three groups (Figure 1). From day 3 there was missing data (as unable to perform tests due to clinical reasons) and most patients had been discharged or had died by day 12. For this reason, no results are presented for day 14 as only a total of 7/44 remained in the ICU.

The obese group had statistically significantly greater initial combined muscle depth compared to the normal weight group, with an average of 3cm greater muscle depth (Table 2). No significant difference in the combined muscle depth loss expressed as cm loss or percentage loss between the groups was seen over day five, seven or twelve.

Table 1 in supplementary information reports the loss for each site (bicep, forearm and thigh). Obese patients had significantly more thigh depth compared to the non-obese patients (0.05). The percentage loss from initial over day 3, 5, 7 and 12 for each site was not different between the groups. The normal patients lost significantly more muscle depth in biceps compared to thighs at day 5 ($p=0.003$). However, this upper and lower limb difference was not observed in the other groups. Regression analysis of the relationship between day seven percentage loss and various independent variables (Table 3) found only gender was significant. When explored further (Supplementary information Table 2), women had significantly less initial muscle depth and lost significantly more at day 7 compared to men.

Nutritional data are shown in Table 3 in the supplementary information. The majority of patients (84%) were fed via the enteral route, the rest receiving parenteral nutrition, a combination of enteral and parenteral or oral nutrition. The mean energy prescription was

significantly less for the obese group compared to the other groups. Irrespective of BMI group, all patients received inadequate energy and protein as compared with their nutrition prescription.

Functional recovery was difficult to assess with an inability of the patient to perform the tasks due to lack of alertness, weakness and poly-trauma. Due to the small numbers no analysis was reported. It was only possible to undertake the MRC sum score and handgrip strength tests in 12/44 patients (27%; normal weight = 4/17; overweight = 2/10; obese = 6/17). The majority of patients were deemed fully dependent with the Barthel Index at days 1 (98%), 3 (90%) and 7 (85%), with only 4 patients out of 27 gaining a score greater than 5 at day 7 of ICU admission.

Discussion

To our knowledge this is the first study to investigate if muscle depth loss observed during critical illness differs between obese, overweight and normal weight patients using a muscle ultrasound technique. The muscle depth loss was comparable and not statistically different between the BMI groups at each of the time points. Increased muscle breakdown in obese patients was seen in the Jeevanadam et al study [13], although patients were not fed for the duration of this study and this may have influenced the rate of muscle breakdown. Direct comparisons cannot be made, as that study used the more precise method of whole body turnover to determine muscle loss compared to the ultrasound technique in our study.

A trial using ultrasound muscle depth to measure muscle wasting in general ICU patients [16] found a decrease of 1.6% per day over seven days and those with the greatest amount of muscle at the start lost significantly more muscle. This was not observed in our study, where women had less muscle to start and lost significantly more. Low admission muscle mass has been shown to be a risk factor for mortality in critically ill patients [30]. Campbell et al [15] studied nine patients with multi-organ failure (MOF) finding a decrease in muscle depth of 6% per day. The muscle loss was considerably higher than the current study and that of Reid et al [16]. This could be explained by illness severity, although Campbell provided no APACHE II or organ failure scores. One can only make assumptions based on the fact that they all had MOF.

The idea that there is a relationship between the degree of organ failure and rates of muscle loss is developed further in the largest published muscle ultrasound study of ICU patients [31]. Muscle mass decreased significantly at day 7 and was significantly greater in patients who experienced multi-organ failure by day 7 (losing 15.7%) compared with 3% loss with single organ failure. Our findings were comparable with that of the MOF patients.

We presented our muscle depth loss as a combined score of three sites, and this may give the impression that all muscle groups waste at the same rate. This may not be the case. The different quadriceps muscles have been shown to waste at differing rates [32] and the diaphragmatic muscles wasted faster than quadriceps [33]. In a study that used limb

circumference, muscle atrophy was observed more in the lower limbs compared with upper limbs [34]. Although this method has been found to be inferior compared to USS in a recent systematic review [35]. When we examined loss at each site individually the opposite was found with the normal weight patients experiencing a larger proportionate loss in the biceps compared to thighs. There was no difference between the groups in terms of wasting seen in at each of the three sites. This warrants further investigation in larger patient numbers.

The USS technique was both feasible and a time efficient tool for use at the bedside in a range of BMI categories. It was not possible to undertake measures on nine occasions due to a variety of reasons, including the patient being too agitated, spastic flexion in the legs, skin breakdown, dressings, peripheral cannula and limbs in casts. There was no difference between the groups for reasons that the measures could not be performed. It was more difficult to obtain accurate images in the obese patients but by increasing the scanning depth it was possible in all patients.

Due to low numbers able to undertake the functional recovery measures, the results are of limited value. Despite the MRC score being advocated as a predictor of ICU acquired weakness [18], there are limitations to its clinical usefulness [36]. As in other trials a significant proportion of patients in our study were unable to perform the test [36; 37]. The same was observed with the hand grip test, where many were too weak to even lift the tool. The Barthel score did not appear to be sensitive enough to detect subtle changes in recovery for this group of patients whilst they were in ICU. From our experience we recommend that the use of the MRC score and grip strength are clinically limited in the ICU and are best used once the patient has left the ICU.

The majority of patients were enterally fed, which can be challenging to deliver [38]. Common reasons for inadequate delivery are gastrointestinal intolerance and fasting for a variety of ICU related procedures. The poor nutritional delivery in our study may have influenced the rates of muscle depth lost, although we didn't set out to measure this. In a previous study [16] where energy targets were determined by indirect calorimeter, achieving energy balance made no difference to muscle depth loss. Our findings and work of others [13] do not support the notion that obese patients are able to metabolise their excess fat

stores and preserve muscle mass. Therefore, based on our pilot study findings the practice of underfeeding obese critically ill patients warrants further investigation.

Whilst the study participants are broadly representative of the general ICU population they were recruited from, it is not possible to make any concrete inferences about the generalizability of the results due to the small sample size. A larger study with more power is needed.

Limitations

As it was a feasibility pilot study no power calculation was undertaken, and the numbers recruited were small. We experienced considerable loss to follow up due to relatively short ICU stays whereas we had intended to follow patients for 14 days. The high attrition rate limits the validity and reliability of our results. To facilitate recruitment, patients could be recruited up to day three of admission to ICU, with the majority being recruited on day two. Substantial muscle loss can occur between day one and three, especially in those in multiple organ failure [31]. In our study the majority were not recruited on day one so considerable muscle loss may already have occurred before our baseline measurements were taken. As such our results may under-estimation of the amount and rate of muscle depth loss during the ICU admission. As seen in the Puthecheary study [31], muscle wasting is significantly influenced by the level of organ failure. We did not collect data on numbers of organs failing, which would have aided the interpretation of muscle depth loss in our study.

This study used ultrasound, a practical non-volitional and effect independent approach of monitoring muscle depth changes. Intra and interrater reliability was not performed in this study. However, previous work within our group showed good correlation and agreement, with intra- and inter-rater reliability of 0.984 and 0.965, respectively. Reliability testing was not performed for the MRC scoring. We recommend following a training programme with extensive practice to ensure competency in ultrasound and MRC score techniques, in addition to undertaking reliability testing.

This study categorised patients according to their BMI; doing so relied on weight and heights, which in critically ill patients can be hard to accurately determine [39; 40]. A variety of

methods were employed to get the most accurate measure possible. Experienced ICU dietitians were making the decisions and thus we feel confident that they are unlikely to place the patient in the wrong category. The limitations of BMI should also be acknowledged. As it is a measure of excess weight rather than excess fat, other factors such as age, sex, ethnicity and muscle mass can influence the BMI [41]. These factors were considered when allocating patients to the appropriate BMI group. A patient was not recruited to the study if they had a raised BMI due to an increased muscle mass as opposed to increased adipose stores (as seen with some ethnic groups and those with increased musculature from excess physical training) [41].

Recommendations for future research

This pilot study suggests there may not be a difference in the rates of muscle wasting between BMI groups. It also suggests that women may lose proportionately more muscle mass than men, although the study was underpowered to detect a meaningful difference. These finding need to be confirmed in further, adequately powered studies.

Future studies need to adjust for confounding factors such as age, gender, illness severity score and degree of organ failure, prior nutritional status and the adequacy of nutritional support received. The amount of nutrition support received (energy and protein intake) may influence the rate of muscle depth lost and needs to be investigated further. We recommend employing in-trial strategies to enhance enteral feeding delivery, such as reduced fasting times guidance and management of gastrointestinal intolerance. Finally, to ensure that functional measures of strength and recovery can be performed, patients should be followed up on discharge from ICU.

To conclude, there were no differences in rates of muscle depth lost between ICU patients in different BMI categories in the setting of comparable nutrition support, suggesting a high BMI may not prevent muscle depth loss.

Abbreviations

ICU, intensive care unit; MRC, Medical Research Council; BMI, body mass index; Dual energy xray absorptiometry; Acute physiology and chronic health evaluation II, APACHE II

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Transparency Declaration

The lead author confirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with STROBE guidelines.

Table 1. Baseline characteristics of patients

Characteristics	Normal (BMI 19-24.9)	Overweight (BMI 25-29.9)	Obese (BMI ≥ 30)
Number	17	10	17
Median (IQR) Age (years)	53(29)	65(16)	55(15)
Gender – Male (%)	13 (77%)	6 (60%)	14 (82)
Median (IQR) BMI	22 (4)	28 (2.5)	33 (1)
Diagnosis: Surgical Medical Trauma / head injury	 4 7 6	 2 5 3	 4 8 5
Comorbidities: Limited nil or 1 (%) Multiple >2 (%)	 9 (53) 8 (47)	 3 (30) 7 (70)	 8 (47) 9 (53)
Median (IQR) APACHE II score	20(7)	22(7)	20 (10)
Median (IQR) Length of ICU stay (days)	16(17)	7(6)	11(9)
Median (IQR) Duration of mechanical ventilation (days)	7(9)	4 (4)	7(10)
% Mortality (deaths/total number)	11.7% (2/17)	40% (4/10)	35% (6/17)

BMI body mass index (Weight kg/height M^2), IQR interquartile range, APACHE II acute physiology and chronic health evaluation

No statistically significant differences between any of the groups. All P values > 0.05

Table 2: Measurements of muscle depth changes during critical illness

Outcome	Normal Weight (n=17)	Overweight (n=10)	Obese (n=17)
Median (IQR) Initial muscle depth (cm)	8.19(2.8)*	8.90 (3.8)	11.15 (3)*
Muscle loss as % (IQR) from initial at:			
Day 5	10.1 (11.4)	11.0 (9)	8.5 (12.8)
Day 7	14.9 (19.5)	17.9 (19.8)	19.7 (18.5)
Imputed Day 7	11.6 (14.4)	17.9 (19.8)	15.6 (16.6)
Day 12	15.9 (11.8)	32.2 (0)	26.8 (3.6)
Median (IQR) Muscle loss (cm) at:			
Day 5	0.88 (1)	1.2 (0.8)	1.13 (1.6)
Day 7	1.49 (1.6)	2.08 (1.7)	2.39 (2.2)
Imputed Day 7	1.11 (1.7)	1.62 (1.5)	2.04 (2.2)
Day 12	1.44 (1.4)	4.14 (0)	2.85 (0.7)
% loss (IQR)per day at:			
Day 5	1.7 (1.9)	1.8 (1.5)	1.4 (2.1)
Day 7	2.5 (3.3)	3.0 (3.3)	3.3 (3.1)
Imputed Day 7	1.9 (2.4)	3.0 (3.3)	2.6 (2.7)
Day 12	2.6 (2.0)	5.4 (0)	4.5 (0.6)

See Figure 1 for number of participants in each group at each time point.

Imputed day 7 – If day 7 values were missing, day 5 values were assumed to be equal and therefore multiple imputation applied.

The day is the study day (not time from admission). i.e. days 5,7,12 from first data collection.

*Initial muscle depth - P 0.006 between normal and obese

For other values no statistically significant differences between any of the groups. All P values > 0.05

Table 3. Regression analysis of relationship between D7 % muscle depth loss and various independent variables.

Variable	Univariate			Multivariate		
	Coef	P values	CI	Coef	P values	CI
Baseline BMI - Overweight - Obese	 0.29 1.8	 0.965 0.700	 -13.0 to 13.5 -7.7to 11.4	 0.29 1.59	 0.96 0.70	 -11.1 to 11.7 - 6.6 to 9.8
Age	3.94	0.357	-4.6 to 12.5			
Gender	-16.0	0.001	-25.1 to 6.9	-15.9	0.002	-25.3 to -6.6
Comorbidities	0.85	0.843	-9.6 to 7.89			
APACHE II	2.67	0.597	-6.4 to 10.9			
Thickest muscle depth D1	0.87	0.841	-9.6 to 7.88			

Coef indicates Coefficient

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