Appetite during the recovery phase of critical illness: a cohort study

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Running title

Appetite in ICU survivors

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Abstract

Background/Objectives: Reduced appetite is a recognised physiological symptom in survivors of critical illness. Whilst reduced appetite has been reported by patients after ICU, quantification using visual analogue scales has not been previously performed, and follow-up duration has been limited. We aimed to describe appetite scores in ICU survivors during the first three months post ICU discharge and explore association with systemic inflammation.

Subjects/Methods: Secondary analysis of data collected in a complex rehabilitation intervention trial (RECOVER). A subgroup of 193 patients provided specific consent for inclusion in the blood sampling sub-study during consent for the main study. We studied appetite using a visual analogue scale (VAS); serum C-reactive protein (CRP); interleukin 1β and 6 (IL-1β and IL-6); and hand-grip strength (HGS).

Results: Median (IQR) score on 0-10 appetite visual analogue scale was 4.3 (2.0-6.5) 1 week after ICU discharge, improving to 7.1 (4.6-8.9) by 3 months (mean difference 1.7 (0.9-2.4) $p<0.01$). Number of days spent in an acute hospital following an intensive care stay was associated with poorer appetite scores ($p=0.03$). CRP concentration and appetite were significantly associated at 1 week after ICU discharge ($p=0.01$), but not at 3 months after ICU discharge ($p=0.67$).

Conclusions: ICU survivors experience reduced appetite during the acute recovery phase of critical illness that could impact on nutritional recovery and this was associated with CRP concentration 1 week after ICU discharge.

Introduction

Survivors of critical illness suffer physical weakness caused by acquired neuromuscular deficits often superimposed on pre-existing frailty ([1]). Skeletal muscle loss is is part of this deficit and occurs early during critical illness ([2,3]). Efforts to improve physical outcomes have so far been unsuccessful ([4-10]). Optimising nutritional state during the recovery phase of critical illness is an

integral part of physical rehabilitation and reduced appetite at this time may impact on nutritional intake.

Malnutrition is observed frequently in ICU patients with many (43%) beng clinically malnourished on admission ([11]). Nutritional status declines during critical illness, and on the post-ICU ward ([11,12]). Malnutrition is associated with muscle loss and functional decline ([13-16]). Optimal nutritional support for ICU survivors is therefore crucial to post-ICU recovery ([17]).

During the early recovery period (during the first 7 days after tracheal extubation), patients do not achieve their calorific targets, and consume fewer than 50% of their estimated protein requirements ([18]). ICU survivors also fail to meet their nutritional targets up to three months after ICU discharge ([19]). Poor appetite during this period has been shown to be an important barrier to eating ([18]).

The mechanisms underlying appetite suppression in survivors of critical illness remain unclear. Ghrelin, a 28 amino-acid peptide released from the stomach is an important regulatory hormone controlling appetite and metabolism in humans ([20]). There is conflicting evidence regarding serum ghrelin concentrations in critically ill patients with some studies reporting decreased circulating levels of ghrelin and others higher ghrelin concentrations compared with healthy controls ([21,12]). Pro-inflammatory cytokines, have a central depressive effect on both food intake ([22]) and appetite ([23]). A recent inflammatory biomarker study showed that there was a high prevalence of systemic inflammation after ICU (70% at ICU discharge and 30% at 3 months) suggesting a prolonged inflammatory response ([24]). We hypothesise that inflammation during recovery from critical illness suppresses appetite, and could have an important impact on physical outcome.

In this analysis we aimed to study the longitudinal course of appetite scores after ICU discharge. A secondary aim was to explore the relationship between appetite and biochemical markers of systemic inflammation.

Materials/Subjects and Methods

Ethics

This study was approved by the Scotland 'A' research ethics committee and conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Patients

The RECOVER study was a randomised trial of increased hospital-based physical rehabilitation versus standard ward care for survivors of critical illness. The trial protocol and main results have been previously published ([4, 25]).

Briefly, patients were eligible for RECOVER if they were adult survivors of critical illness, were ventilated for greater than 48 hours and were deemed fit for ICU discharge by the treating physician. Exclusion criteria included a primary neurological diagnosis, receipt of palliative care, receipt of home ventilation or under 18 years of age.

At recruitment into the study patients were randomised into either the control or intervention group. Both groups received existing ward-based physiotherapy, dietetics, occupational and speech/language therapy until hospital discharge. The intervention patients received enhanced hospital-based physical rehabilitation that increased the frequency and intensity of rehabilitation during their ward stay. This was delivered by a generic rehabilitation assistant (GRA) with nutritional interventions including support and encouragement to eat and greater attention to monitoring of nutritional intake.

The between-group comparison of outcomes in the trial found no clinically or statistically significant differences in measures of physical function, health-related quality of life (HRQoL), psychological morbidity or self-reported symptoms ([25]), and therefore the patients were treated as a single group for the purpose of this analysis.

A subgroup of 193 patients provided specific consent for inclusion in the blood sampling sub-study during consent for the main study.

Measurements

Appetite was assessed in study participants 1 week after study entry (equating to 1 week after ICU discharge), weekly until hospital discharge, and again at a follow up appointment 3 months after study entry. In those patients discharged from hospital during the follow up period i.e. those that did not die in hospital (death in hospital = 4 patients) or were not still in hospital 3 months after enrolment (inpatient at 3 months = 12 patients), appetite scores were reported at hospital discharge.

Appetite assessment was conducted using a 10 centimetre visual analogue scale (VAS). At each end of the line words described the minimum and maximum extremes of the characteristic being measured with the low end to the left on a horizontal scale ([26]). Individuals were asked to mark on the line at the point they felt indicated how they were currently feeling. The score was determined by measuring the distance from the left hand end on a horizontal scale to the point marked by the individual ([27]). VAS are a reliable and reproducible tool for assessing appetite ([28]), however it has not been validated in the post ICU patient population.

To explore the medium-term nutritional consequences of appetite suppression on nutritional status, we measured hand-grip strength 3 months after study enrolment ([29]).

We measured the serum concentration of C-reactive protein (CRP), interleukin 6 (IL-6) and interleukin 1β (IL-1β) by ELISA (R and D systems) to detect the presence of on-going inflammation during the recovery phase of critical illness. For this study, blood was analysed at two time points corresponding to the first appetite assessment and the 3 month follow up assessment.

Statistical Analysis

VAS appetite scores had a non-parametric distribution and are presented as medians with interquartile ranges for each time point. Paired differences between baseline and follow up samples were normal in distribution and a t-test was applied to compare this difference to zero.

To explore the association between inflammation and appetite, we calculated Kendall's tau correlation co-efficient for the VAS appetite score and inflammatory biomarkers at the time of the first appetite assessment (1 week after study entry), and follow up (3 months after study entry).

To explore the medium-term functional consequences of appetite suppression we tested the association between appetite score at hospital discharge, and hand grip strength at the 3 month follow up stage using the Spearman's rho correlation co-efficient. In addition, the sample was divided into 2 groups above and below the median appetite VAS score. The mean hand grip strength in each of these groups was compared using an independent samples t-test. To take into account the effects of age and gender on hand grip strength, percentage predicted hand-grip strength was calculated using population norms derived from a previous study ([30]) and the above analysis repeated.

The correlation coefficients used in the analysis were selected on the basis of distributions and can be justified (data not shown).

Results

Patients and completeness of data

240 patients were recruited to the RECOVER study between December 2010 and January 2013. 228 (95%) were followed up to 3 months. The baseline characteristics of the cohort are described in Table 1. At the time of first assessment (1 week after study entry), 152 patients had appetite VAS score measured. At final assessment, 188 patients had appetite VAS score measured.

193 patients (80%) gave consent for inclusion in the blood sampling sub-study. At the first assessment (1 week after study entry), 109 patients had CRP, IL-1β, and IL-6 measured. At the final assessment, 123 patients had CRP measured, 120 patients had IL-6 and 120 patients had IL-1β measured.

Appetite

Appetite scores at each time point are presented in Figure 1. Median VAS appetite score was low (below 5cm) at each time point until after ICU discharge. There was an improvement in appetite from a median (IQR) of 4.3 (2.0-6.5) to 7.1 (4.6-8.9) during the first 3 months. The mean (95% CI) for this difference was 1.7 (0.9 – 2.4) (p=0.000).

To illustrate change in appetite over time, patients available for assessment at both baseline and 3 months (n=130) were divided into 4 groups according to their appetite scores. The percentage of patients within each group at each time point are illustrated in Figure 2.

Post-hoc analysis

For patients staying in hospital for many weeks after ICU discharge appetite scores appeared to be particularly low (Figure 1). To explore this further, mean appetite scores were calculated for each

patient during their post-ICU hospital stay and the correlation between the number of days in hospital after enrolment in RECOVER, and mean appetite score during hospitalisation was calculated. Spearman's rho was -0.231 (p=0.030) for this correlation suggesting that patients who spent longer periods in the acute hospital post ICU discharge was associated with poor appetite. To illustrate this point, Figure 3 shows the appetite scores in the weeks following ICU discharge for patients who spent ≤5 weeks in hospital (n=130) versus those spending >5 weeks in hospital (n=30). Note those patients discharged home prior to 1 week after enrolment had no appetite score measured in hospital and were not considered.

In the patients that were discharged from hospital alive (n=141), the median (IQR) appetite VAS was 5.0 (3.0-8.0) at hospital discharge.

Appetite and functional outcome

There was no significant association between appetite at hospital discharge and predicted handgrip strength at the 3-month follow up point (Pearson Correlation 0.032; p=0.756).

Appetite and inflammation

A summary of the analysis is given in Table 2. There was a significant correlation between CRP concentration and appetite VAS at the first assessment point (Kendall's tau B -0.159 (p=0.018). At the 3-month assessment, the correlation was not significant (Kendall's tau B -0.026; p=0.67). There was no significant association between IL-6 at first or follow up assessment. IL1- β was undetectable in the majority of patients throughout the study and therefore formal tests of correlation were not conducted for this molecule.

Discussion

Appetite suppression

In this paper we confirm the findings of previous studies that identified appetite suppression to be a significant symptom in the early days of post-ICU recovery. In addition, we have shown that loss of appetite is sustained during the period of post-ICU hospitalisation.

In contrast to previous studies, we have also identified appetite suppression at the point of hospital discharge, a crucial transition in the nutritional care of ICU survivors. Although hospital discharge defines the point where patients are physically able to cope with some activities of daily living, it is also the point when the acute care rehabilitation, including dietetic input ceases ([31]) and a time when even modest dietetic input can lead to nutritional and functional gains ([32]).

Nutritional care is a key component of physical recovery after critical illness ([17]). Traditional approaches to nutritional rehabilitation focus on supplementing hospital food to achieve nutritional targets, approaches that fail when appetite is suppressed and patients have little inclination or motivation to eat ([12]). With the knowledge that ICU patients suffer sustained appetite suppression, efforts to improve post-ICU nutritional status must now focus on efforts to improve or circumvent appetite suppression. In addition, greater efforts must be made to equip patients with information and advice to help them recognise and overcome this common and limiting symptomatology after hospital discharge.

Pharmacological modification of appetite in these patients may be possible in the future. Recent animal studies have suggested the potential role of ghrelin as a future potential therapeutic utility to stimulate feeding and growth hormone secretion by promoting gastric peristalsis and generating hunger sensations ([33,34]) In healthy humans, higher levels of ghrelin are seen during periods of fasting and vice versa after meal, which are associated with elevated insulin and low glucose levels ([20,33,36]). There is a paucity of data with regard to the relationship between appetite and calorie intake with ghrelin levels after ICU discharge.

More practical measures to promote nutritional intake in patients with poor appetite include offering small frequent meals and the provision of energy dense foods ([37]). Previous work has shown that providing three meals a day is seen as a deterrent to post ICU patients with small appetites who find larger meals off-putting ([31]).

The social nature of eating is an important contributor to increased food intake with energy intakes increased by 36% in patients using a dining room compared to those who ate beside their bed ([38]). However, the application of this solution may require some creativity in a post-ICU cohort, many of whom may be nursed in isolation for infection control reasons or experience reduced mobility due to critical illness related muscle weakness.

The effect of exercise on appetite has been widely studied with a body of evidence suggesting that an acute bout of exercise does not result in an increase in appetite and food intake ([39-41]). It is now widely reported that vigorous exercise can transiently suppress appetite ([42]) however this response is short lived and is not observed in low or moderate intensity exercise ([43]). In the RECOVER study ([25]) there was no difference in appetite at 3 months between the intervention and control groups, but we were unable to assess the impact of exercise frequency or intensity on appetite.

Critical illness is characterised by systemic inflammation, a defensive response carefully regulated by circulating inflammatory cytokines. In many patients inflammation is sustained beyond ICU discharge ([24]). Previous studies have shown a possible role for inflammation in appetite suppression in non-critically ill populations. Patients undergoing haemodialysis have appetite suppression in association with higher concentrations of pro-inflammatory cytokines ([44]). Poor appetite was also linked to increased mortality, higher rates of hospitalisation and reduced quality of

life. Similar findings have been shown in patients with advanced cancer where increased levels of inflammation were associated with a number of symptoms including pain, fatigue and anorexia ([45]).

One of the best-described pro-inflammatory cytokines is interleukin 1β, which is known to exert a profound depression of appetite mechanisms ([23]). Unfortunately, in our study IL1- β was undetectable in the majority of patients, therefore we were unable to include this molecule in our analysis. Tumor-necrosis factor-α (TNF- α) and interleukin-6 are the other pro-inflammatory cytokines known to induce anorexia ([46]). The mechanisms by which these cytokines affect the central nervous system controls of food intake are not fully understood ([22]). Through signalling in the hypothalamus, the pro-inflammatory cytokines activate neuro-pathways that repress the desire for food. These cytokines also activate signalling from the autonomic nervous system modulating gastric motility and emptying. Additionally the cytokines stimulate the release of hormones that suppress food intake such as leptin and insulin ([47]).

In our study, we found that patients with higher C-reactive protein concentrations soon after ICU discharge had poorer appetite scores suggesting a potential role for systemic inflammation in post intensive care appetite suppression, but found no association between CRP and appetite at 3 months or IL-6 and appetite at either 1 week or 3 months.

In previous work, we explored risk factors for appetite at 3, 6, and 12 month time points after ICU and found illness severity to be insignificant when compared to pre-ICU factors ([48]). Whether this is the case for earlier time points remains unknown, but certainly the association with pro-inflammatory mediators suggests that ongoing pathology may play a role.

There are several weaknesses of the study. First, this is a post-hoc analysis and the original RECOVER trial was not powered to detect the correlations explored. Second, our measure of

appetite has not been used in this cohort previously and we have no control group to compare our patients to. It is therefore difficult to determine whether the appetite scores noted in our results could be considered normal, poor, or good. Third, we did not measure oral intake or calorific consumption in this study so could not assess the impact of appetite suppression on eating behaviour. Fourth, the cohort is representative of a ventilated mixed medical/surgical cohort, but it is worth noting that a significant proportion had a GI diagnosis, potentially resulting in more severe appetite suppression, depending on the comparator population.

Conclusions

ICU survivors experience a supressed appetite during the acute recovery phase of critical illness. Inflammation was found to be associated with appetite at time points close to ICU discharge suggesting possible modifying effect of systemic inflammation on appetite in the early post-ICU period, a crucial time for nutritional intervention. Nutritional management of ICU survivors should include ways to maximise intake in order to help circumvent the suppression of appetite encountered by this patient group, and modification of the inflammatory response may be a future avenue for investigation.

Conflict of Interest

The authors declare that they have no conflicts of interest. The RECOVER trial on which this analysis is based is registered as ISRCTN09412438. The RECOVER trial work was supported by the Chief Scientists Office, Scotland

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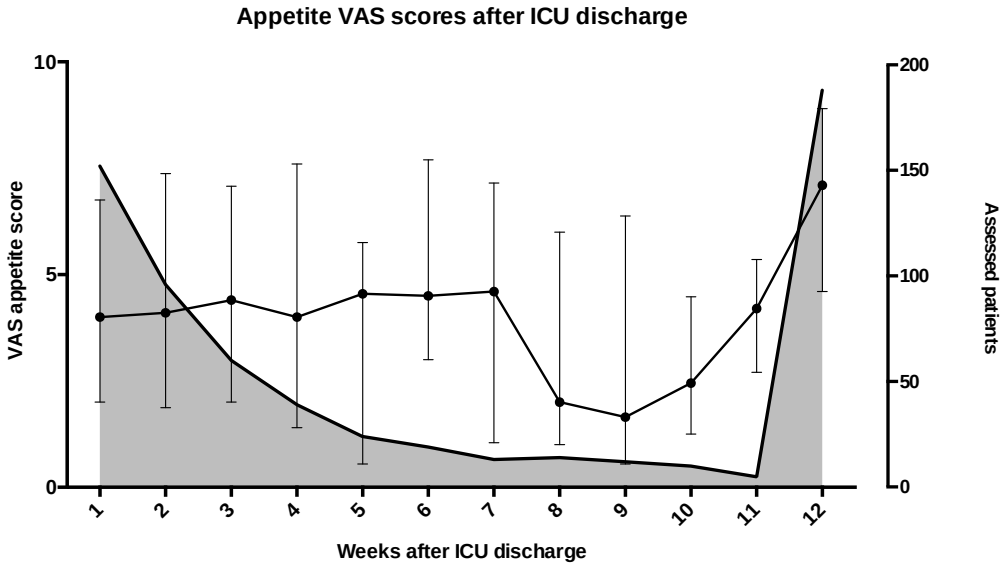
Table 1: Participant characteristics at randomization.

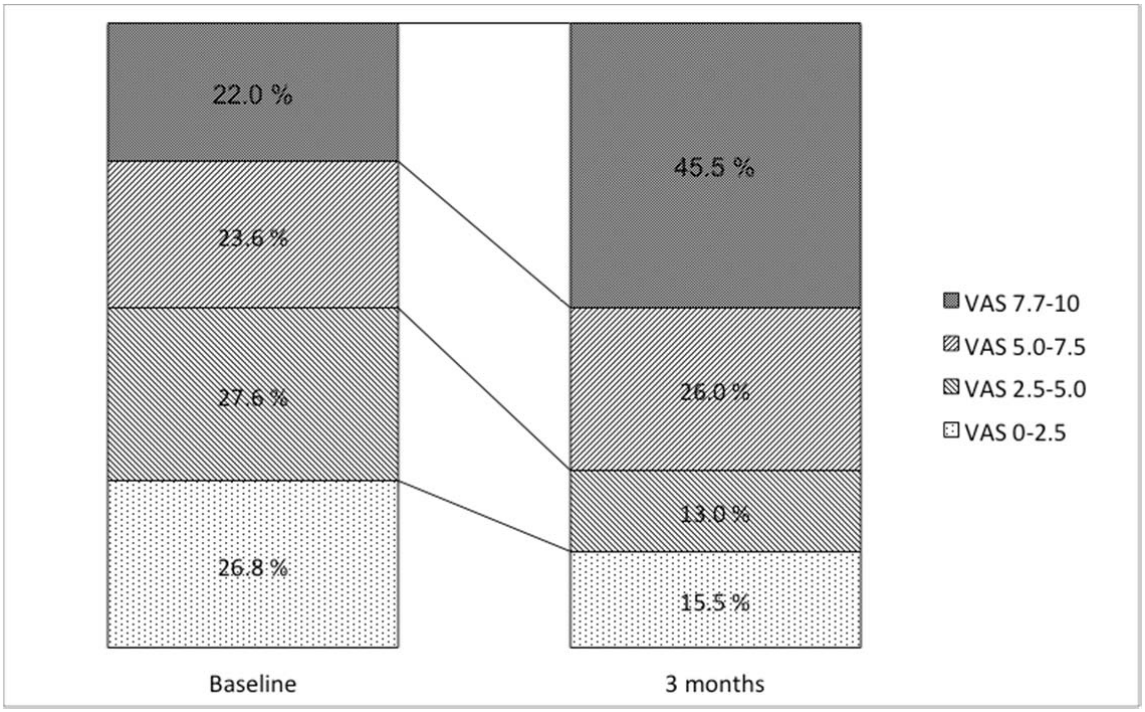
Table 2: Kendall's tau correlation coefficients of inflammatory biomarkers with appetite visual analogue scores.

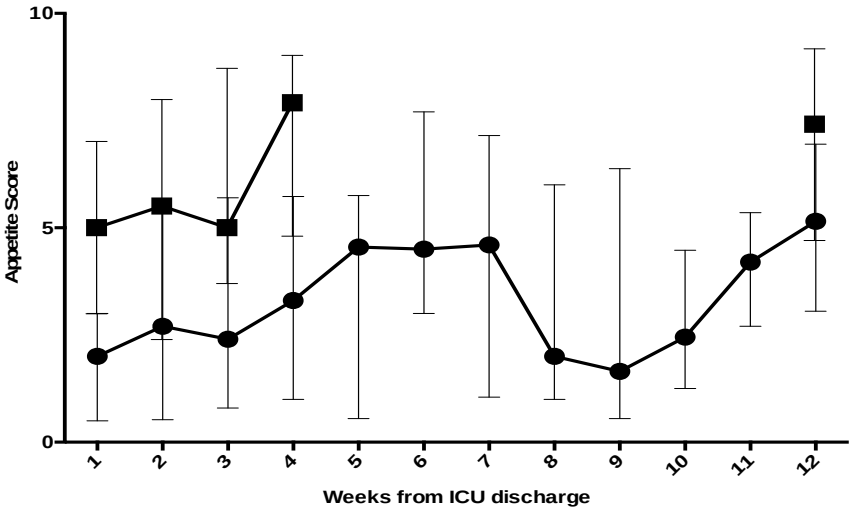
Figure 1: Appetite scores by week after ICU discharge. Grey shading indicates the number of patients assessed at each time. Only patients remaining in hospital had appetite VAS recorded which explains the decline in n number but we aimed to assess all patients surviving to 3 months.

Figure 2: For patients with complete data, change in appetite score category between baseline and 3 months (n=130 patients).

Figure 3: Appetite scores after ICU discharge (median (IQR)). Square markers denote patients staying in hospital up to 5 weeks after ICU discharge (n=130). Round markers denote patients staying in hospital greater than 5 weeks after ICU discharge (n=30).


Appetite VAS scores after ICU discharge
VAS appetite score
Assessed patients
Weeks after ICU discharge
10
5
0
200
150
100
50
0
1
2
3
4
5
6
7
8
9
10
11
12


22.0 %
23.6 %
27.6 %
26.8 %
45.5 %
26.0 %
13.0 %
15.5 %
Baseline
3 months
VAS 7.7-10
VAS 5.0-7.5
VAS 2.5-5.0
VAS 0-2.5


10
5
0
Appetite Score
1
2
3
4
5
6
7
8
9
10
11
12
Weeks from ICU discharge

	RECOVER cohort (n=240)
Male N (%)	137 (57)
Age (median (1^{st} ;3^{rd} quartiles))	62 (52, 70)
Days of ventilation in ICU (median (1st ;3rd quartiles))	8 (5,15)
APACHE II score (median (1st ;3rd quartiles))	20 (16,25)
ICU admission diagnosis category N (%)	
Respiratory	84 (35)
Cardiovascular	70 (29)
Gastrointestinal	59 (25)
Neurological	12 (5)
Trauma	8 (3)
Renal diagnosis	4 (2)
Miscellaneous diagnoses	3 (1)
Well-nourished N (%)	107 (45)
Moderately malnourished N (%)	105 (43)
Severely malnourished N (%)	28 (12)
Ward destination N (%): Medical	135 (56)
Surgical	105 (44)

		Kendall’s tau	p
CRP	1 week	-0.159	0.018
	3 months	-0.026	0.676
IL-6	1 week	-0.122	0.271
	3 months	0.008	0.897