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Protocol

Metabolism and the impact of protein intake in Chronic critically ill adult patients: Protocol for a unicentric prospective cohort study (MetaChronic Study)

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SUMMARY

Background: Survival of acutely critically ill patients has improved, resulting in a growing population of chronic critically ill (CCI) patients with prolonged organ dysfunction, mechanical ventilation, and high morbidity. While nutritional guidelines during the acute phase of critical illness are well defined, our understanding of metabolism and nutritional needs in CCI patients is limited. Persistent inflammation may influence the metabolic response and nutritional uptake, highlighting the need for prospective studies in this area.

Methods: The MetaChronic Study is a single-center, prospective cohort study of metabolism in patients with CCI. Adult ICU patients with invasive mechanical ventilation ≥48 h and ICU stay >7 days are eligible. Patients are followed for up to 42 days after ICU admission, with final outcomes assessed at 90 days. Resting energy expenditure is measured weekly by serial indirect calorimetry. Weekly protein and calorie intake are recorded and inflammation is assessed using serum C-reactive protein and procalcitonin measurements. Patients are categorized according to high or low protein intake (>1.3 g/kg/day vs. ≤1.3 g/kg/day after the first week). The primary objective is to characterize longitudinal metabolic trajectories. Secondary objectives include subgroup analyses (septic, trauma, neurocritical patients), assessment of the interaction between inflammation and metabolic rate, and exploratory analyses of the association between protein intake and clinical outcomes.

Ethics and dissemination: The study has been approved by the institutional ethics committee. Findings will be disseminated through peer-reviewed journals and scientific conferences.

1. Introduction

Improvements in organ support and intensive care unit (ICU) clinical practice have led to an increase in survival during the acute phase of critical illness [1]. However, many patients require persistent organ support even after the acute phase of illness has passed, a subgroup known as the 'chronic critically ill'. Typically, these patients have long periods of invasive mechanical ventilation (IMV), are often tracheostomized, have acquired muscle weakness, repeated nosocomial infections and experience long periods of suffering [2].

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One of the most widely accepted definitions of chronic critical illness (CCI) is that of Kahn, who specified an ICU stay >7 days associated with one of the following six conditions: prolonged mechanical ventilation, tracheostomy, stroke, traumatic brain injury (TBI), sepsis, or intracranial hemorrhage [3]. Other investigators have specified even longer periods of ICU admission (14 or 21 days), usually accompanied by prolonged mechanical ventilation [2].

Studies have shown that in critical illness there are complex interactions between the precipitating disease (aggression), genetic factors, inflammation and neuroendocrine factors. In most patients, however, the pro-inflammatory and catabolic state of acute critical illness resolves after treatment of the inciting illness and a period of anabolism and progressive recovery of dysfunction begins. Patients with CCI, however, remain in a persistent inflammatory and catabolic state even after the initial insult is treated. Further complicating the study of CCI patients is a high degree of heterogeneity and the existence of different metabolic phenotypes [4].

The metabolic profile of critically ill patients in the acute phase is well documented. Given their underlying catabolic state and the negative impact of nutrition on adaptive responses such as autophagy [5], there is general agreement that excess calorie intake in this phase is harmful [6]. After the first week of critical illness, however, there is a lack of data on metabolism as well as the impact of different nutritional strategies on outcomes. In particular, it is unclear when and to what extent protein and calorie intake should be increased in order to optimize outcomes [7–9]. Currently, European guidelines recommend protein intake of 1.3 g/kg/d by the end of the first week of critical illness [10,11]. However, there are no guidelines for protein or calorie intake beyond the first week, nor for patients with persistent inflammation and CCI. There is therefore a recognized need for robust studies of metabolism and nutrition amongst CCI patients in order to better define nutritional goals for these patients [9,12] and facilitate their recovery and rehabilitation [13].

2. Objective

This study will characterize longitudinal changes in metabolism and inflammation amongst patients with chronic critical illness and will analyze their relationship to clinical outcomes. It will further assess the impact of different protein strategies on metabolism, inflammation and patient outcomes.

The objectives of the MetaChronic study are summarized in Table 1.

3. Methods

This is a single-center, longitudinal, prospective observational study. Adult critically ill patients who have been admitted for more than 7 days in the intensive care unit (ICU) and have received invasive mechanical ventilation (IMV) for at least 48 h will be recruited. Enrolled patients will be followed in-hospital up to 6 weeks (42 days) after ICU admission until discharge or death. Follow-up will be suspended when it is no longer possible to accurately assess nutritional intake (i.e. when oral feeding begins), excluding oral intake for swallowing training or sensory stimulation. Follow-up will also be suspended if the patient's initial ICU admission is shorter than 14 days. Long-term follow-up assessment will take place 90 days after ICU admission when functional status will be characterized using the validated Portuguese version of the EuroQol 5-Dimensions (EQ-5D) scale. If the patient is no longer admitted to the study center, follow-up will take place over the phone (telephone version of the EQ-5D scale).

Patients will be characterized according to demographic data (age, gender), pre-existing clinical status (days of hospitalization prior to ICU admission; nutritional risk score determined by the Nutric score without Interleukin-6); and ICU admission characteristics (illness subgroup [septic with/without abdominal surgery, trauma with/without head trauma; neurocritical; others], and severity of illness on admission according to the Simplified Acute Physiology Score II [SAPSII]). Illness subgroups will be defined as follows:

- Septic: patients admitted with sepsis or septic shock according to Sepsis-3 criteria, subdivided into those requiring abdominal surgery and those who did not.
- Trauma: patients admitted following trauma requiring ICU admission, subdivided into those with traumatic brain injury and those without.
- Neurocritical: patients admitted for non-traumatic neurological diagnoses, primarily including spontaneous intracranial hemorrhages.
- Others: patients whose admission diagnosis does not fall into the above categories.

To determine resting metabolic rate, serial indirect calorimetry (IC) will be performed from the 7th day of ICU stay until hospital discharge (or 42 days if still hospitalized at that time) at least once per week, when feasible. To be eligible for calorimetry, patients must not have chest tubes or significant air leaks in their ventilatory circuit. For technical reasons, they must either be on invasive mechanical ventilation (IMV) or breathing spontaneously without the need for oxygen supplementation. For patients on IMV, the inspiratory oxygen fraction (FiO_2) should be <70 % and the end-expiratory pressure (PEEP) should be < 12 cmH_2O, as per the manufacturer's recommendations (QNRG, Cosmed). For patients who are spontaneously ventilating, the FiO_2 should be 21 %. The weekly average will be calculated as the mean of all measurements during a given week.

Table 1
Primary and secondary objectives of the study.

Primary objective	1. Characterize the resting metabolic rate of chronic critically ill patients during the first 42 days of intensive care admission.
Secondary objectives	1. Compare the resting metabolic rate of different subpopulations of chronic critically ill patients during the first 42 days of ICU admission: Septic, trauma, neurocritical, and others. 2. Analyze the association between protein intake (above or below 1.3 g/kg/day) in CCI and clinical outcomes (Table 2). 3. Analyze the association between protein intake and outcomes in chronic critical illness taking into account the following variables: a. Resting metabolic rate b. Route of protein administration (enteric, parenteral, and mixed) c. Patient subpopulation (septic, trauma, neurocritical, and others) d. Inflammation (CRP and procalcitonin levels). e. Calorie intake

CCI: Chronic Critical Illness; CRP: C-reactive protein.

Protein intake will be prescribed by the clinical team, in keeping with European guidelines for critically ill patients, individualized by body weight and clinical condition, and recorded weekly in grams per kg of adjusted body weight (adjusted body weight = ideal body weight + 0.25 × [actual weight − ideal body weight]), with separate accounting for enteral, parenteral, or mixed routes. Grams of amino acids (AA) will be converted to grams of protein using the conversion factor of 100 g of hydrolyzed protein to 83 g of AA.

In line with the core outcomes recommended by CONCISE [14], patients will be classified according to protein intake during the second week of ICU admission: those receiving >1.3 g/kg/day versus ≤1.3 g/kg/day. Only patients alive and still in the ICU at the end of the second week will be included in this comparison, using the second week as the reference time point. This landmark approach inherently restricts the analysis to patients surviving and remaining evaluable at the end of week two, a limitation that will be taken into account when interpreting associations with clinical outcomes. The following outcomes will be assessed:

- Duration of invasive mechanical ventilation (days);
- ICU and hospital length of stay (days);
- Days alive and out of the ICU to day 90 (days);
- Days alive and out of the hospital to day 90 (days);
- Need for tracheostomy (Y/N); If yes, possibility of decannulation (Y/N); Duration of tracheostomy (days);
- Mortality at 28 days and in-hospital;
- Number of infections to day 30 (This is defined as the number of infectious agents, not deemed to be colonization, in biological samples performed in accordance with local standard practice).
- Discharge destination (institution/home);
- Functional outcome at day 90 (EQ5D scale and mortality)

Inflammatory state will be characterized weekly as the median of daily C-reactive protein (CRP) and procalcitonin values. Exploratory analyses may consider all daily measurements over time using longitudinal modeling to assess trends and associations in more detail.

Total caloric intake will be calculated weekly based on documented nutritional support (enteral and parenteral formulas), as well as caloric intake from non-nutritional therapies, such as glucose infusions and propofol.

This study is registered at ClinicalTrials.gov (NCT07268274).

3.1. Population

The study will include adult critically ill patients admitted to intensive care unit who meet the eligibility criteria described below:

3.1.1. Inclusion criteria

Adult critically ill patients admitted to ICU >7 days with invasive mechanical ventilation (IMV) > 48 h.

3.1.2. Exclusion criteria

Active oncological disease.

Neuromuscular disease.

Confirmed or predicted Glasgow Coma Score <10 at 14 days in ICU.

Pregnant women.

3.2. Variables description

The variables are listed and described in Table 2.

Figure 1 provides a schematic overview of the study design.

3.3. Data management

Patient data will be obtained from the electronic clinical record and will be recorded in a database, anonymized and with a secret access code, under the responsibility of the Principal Investigator. The study will be conducted in accordance with good clinical practice, ethical principles and Portuguese legislation on clinical research. Patients will be recruited on the 7th day of admission to the ICU according to the inclusion and exclusion criteria.

Table 2
Characterization of variables.

Demographic Variables	• Age (years) • Sex • BMI (Body Mass Index) on admission to the ICU
Premorbid clinical state	• Length of hospital stay before ICU (days) • Nutric score without IL6 at ICU admission
Illness leading to ICU admission	• Admission diagnosis subgroup: Septic, with and without abdominal surgery; trauma, with and without TBI; neurocritical (without associated trauma); others • Severity on admission: SAPS II index
Metabolism	• Average weekly resting energy expenditure (REE) in kcal per day
Protein intake	• Protein intake (± 1.3 g/kg weekly average) • Grams of protein supplied per kg of weight (ideal weight or adjusted if BMI >30 or < 18 on admission) (daily average per week) • Grams of protein supplied per kg by enteric route • Grams of protein supplied per kg parenterally
Calorie intake	• Calories per kg (ideal weight or adjusted if BMI >30 or < 18 on admission); (daily average per week)
Inflammation	• CRP (weekly median) • Procalcitonin (weekly median)
Outcome variables	• Duration of invasive mechanical ventilation (days) • ICU and hospital length of stay (days); • Days alive and out of the ICU to day 90 (days) • Days alive and out of the hospital to day 90 (days) • Need for tracheostomy (Yes/No); if yes, possibility of decannulation (Yes/No); Duration of tracheostomy (days) • Mortality at 28 days and in-hospital • Number of infections to day 30 • Discharge destination (institution/home) • Functional outcome at day 90 (EQ-5D scale and mortality)

BMI: Body Mass Índex; ICU: Intensive Care Unit; IL-6: Interleukin-6; TBI: Traumatic Brain Injury; SAPSII: Simplified Acute Physiology Score II; REE: Resting Energy Expenditure; CRP: C-reactive protein; EQ-5D: EuroQol 5-Dimensions.

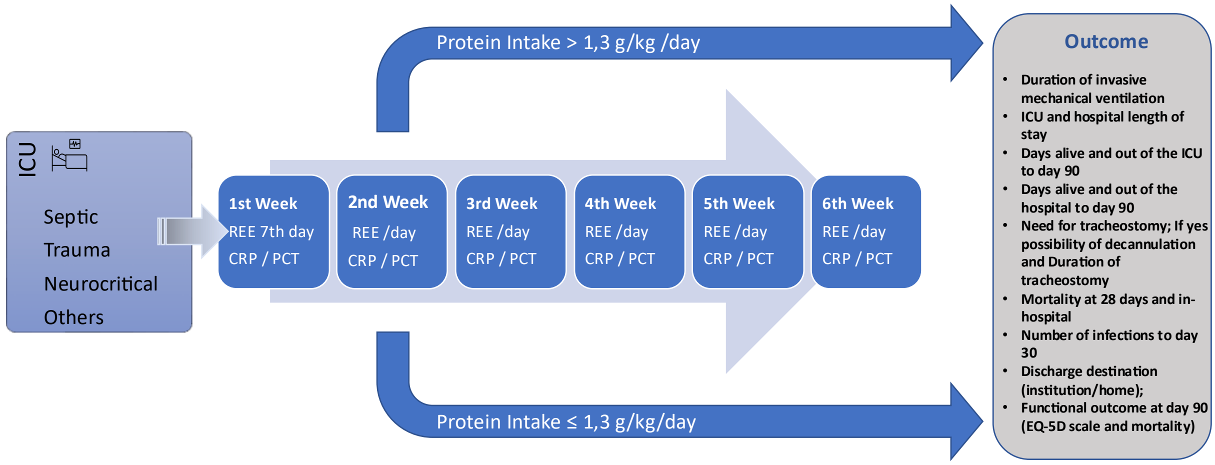

Fig. 1. Schematic representation of the MetaChronic study
ICU: Intensive Care Unit; REE: Resting Energy Expenditure; CRP:C-reactive Protein; PCT: Procalcitonin; EQ-5D: EuroQol 5-Dimensions.

3.4. Sample, population and statistical analysis

3.4.1. Sample size

The anticipated sample size is 100 patients. Based on pilot data, we estimate an average REE of 21 ± 4 kcal/kg/d amongst CCI patients. Given the longitudinal design, a sample size of 100 patients will give >80 % power to detect clinically relevant changes in REE >15 % between weeks 1 and 6 of the study at a significance level of 5 % ($p = 0.05$).

3.4.2. Statistical analysis

All of the clinical and analytical variables will be analyzed descriptively. For continuous variables, the mean and standard deviation or median and interquartile range will be presented, depending on the distribution, along with the maximum and minimum. For categorical variables, absolute and relative frequencies will be presented.

For characterization of REE over time we will subdivide patients into 3 categories based on their REE in the 2 nd week of study recruitment: hypermetabolic patients will be defined as those with REE ≥30 kcal/kg, normometabolic patients as those with REE ≥20 kcal/kg and <30 kcal/kg, and hypometabolic patients as those with REE <20 kcal/kg. We will perform a descriptive analysis based on REE in week 2 (proportions of hyper/normo/hypometabolic patients) and changes in REE over time (stable, tendentially increasing, tendentially decreasing, heterogeneous). We will also analyze the longitudinal evolution of REE using a mixed-effects model with patients as a random effect (random intercepts, with or without random slopes) and time as a fixed effect. Missing REE measurements, occurring both in more severely ill patients and in patients who rapidly wean from mechanical ventilation, will be addressed using multiple imputation. Sensitivity analyses will be performed to assess the robustness of the findings across different imputation scenarios.

With regard to the secondary objectives: for the comparison of REE between subgroups (septic; trauma; neurocritical), we will conduct a two-way ANOVA to identify between-group differences over time. For comparison of outcomes between patients with high (>1.3 g/kg/d) and low (≤1.3 g/kg/d) protein intake, we will use the Student's t-test to compare continuous variables with normal distribution and Wilcoxon rank-sum test for variables with non-normal distribution. Fisher's exact test will be used to compare categorical variables. For analysis of the association between protein intake and ICU-free and hospital-free days to day 90, we will use Poisson regression. Pre-specified sensitivity analyses will include alternative time horizons (e.g., ICU-free and hospital-free days to day 28 and day 60) as well as alternative approaches to handling death, including ordinal analyses in which death is ranked worse than any number of ICU-free days and competing-risk analyses of time to ICU discharge alive.

Statistical significance will be defined as $p < 0.05$.

Ethical considerations and dissemination

The study will be conducted in accordance with good clinical practice standards, ethical principles and Portuguese legislation on clinical research.

The study has been approved by the Ethics Committee of the Local Health Unit where the study will be conducted (UAIF 164/2023).

Findings will be disseminated through peer-reviewed journals and scientific conferences.

Authors' contributions

S. Castro is the corresponding author and was responsible for drafting the manuscript.

A. Binnie assisted with the methods and statistical analysis sections and reviewed the final manuscript.

T. Pires and C. Oliveira assisted with study design.

C. Granja and J. Dionne assisted with study design and reviewed the final manuscript.

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Declaration of competing interest

The author, S. Castro, reports receiving speaker fees from Baxter and conference sponsorship from Fresenius. The remaining authors declare that they have no conflicts of interest relevant to this manuscript.

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