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# A single-centre, cross-over trial evaluating the metabolic effects of a ketone ester food supplement in intensive care patients

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| **Submission date**<br>24/10/2023 | **Recruitment status**<br>Recruiting | [X] Prospectively registered<br>[X] Protocol<br>[_] Statistical analysis plan<br>[_] Results<br>[_] Individual participant data<br>[X] Record updated in last year |
| **Registration date**<br>27/10/2023 | **Overall study status**<br>Ongoing | |
| **Last Edited**<br>23/01/2025 | **Condition category**<br>Other | |

## Plain English summary of protocol

Background and study aims
The majority of long-term critically ill patients develop muscle weakness and muscle wasting during their stay in intensive care, which hampers recovery and leads to increased complications and a greater risk of death. In animal experiments administering a nutritional supplement, namely ketone esters, can improve muscle weakness during disease. The next step in this research is to see if this supplement can be used to prevent or improve muscle weakness in critically ill patients. The first step is to determine a well-tolerated and effective dose of the dietary supplement (ketone esters) in critically ill patients.

Who can participate?
Adults over the age of 18 years who are admitted to the intensive care unit in UZ Leuven

What does the study involve?
This pilot study will test three doses (25 g, 50 g and 75 g) of ketone esters in adult critically ill patients. Participants are randomly allocated to receive the product or a placebo through a nasogastric feeding tube on 2 consecutive days. Frequent blood samples are scheduled to determine at which dose there is an effective increase in ketones in the blood without any adverse side effects.

What are the possible benefits and risks of participating?
There are no known interactions of ketone esters with drugs. Still, it is possible that nausea or abdominal pain, for example, may occur if the dietary supplement is not well tolerated.

Where is the study run from?
University Hospitals Leuven (Belgium)

When is the study starting and how long is it expected to run for?
January 2023 to December 2026

Who is funding the study?
1. European Research Council (ERC)
2. Flemish Government (Belgium)

Who is the main contact?
Prof. Dr. Greet Van den Berghe, greet.vandenberghe@kuleuven.be

# Contact information


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## Additional identifiers

### EudraCT/CTIS number
Nil known

### IRAS number

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
S67928

## Study information

### Scientific Title
A single-centre, placebo-controlled, cross-over randomized controlled trial evaluating the metabolic effects of a ketone ester food supplement in intensive care patients: the KETOCARE RCT

### Acronym
KETOCARE RCT

## Study objectives
To study the feasibility, safety and tolerability of enteral ketone ester supplementation to increase circulating ketone levels in adult critically ill patients.

## Ethics approval required
Ethics approval required

## Ethics approval(s)
Approved 12/09/2023, Ethics Committee Research UZ/KU Leuven (Herestraat 49, Leuven, 3000, Belgium; +32 (0)16 34 86 00; ec@uzleuven.be), ref: S67928

## Study design
Single-center placebo-controlled cross-over randomized controlled trial

## Primary study design
Interventional

## Secondary study design
Randomised cross over trial

## Study setting(s)
Hospital

## Study type(s)
Safety, Efficacy

## Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

## Health condition(s) or problem(s) studied
Adult critically ill patients

## Interventions
A blocked randomization scheme with blocks of 4 patients will be used in this study. The code for randomization blinding is stored in the randomization tool, developed in FilemakerPro with restricted access to the database administrators. Randomization will be carried out by dedicated research staff members using a role-based user access.

With a cross-over design, patients will receive in random order on 2 consecutive days ketone ester (3HHB) and a placebo (5% glucose). The ketone esters will be supplied by TDeltaS Ltd (UK).

Patients will receive the investigational product between ICU days 4 and 10. The investigational product (3HHB) or placebo will be delivered through the enteral feeding tube via repeated small boluses. The researchers will first perform this trial with a 25 g dose of 3HHB divided over 6 boluses of 3,9 ml. Next, they will assess the primary and secondary endpoints in this cohort of patients. If the dose of 25 g is found safe but ineffective for increasing plasma 3-hydroxybutyrate at least with 0.22 mmol/l, a second cohort of patients will be tested with the same cross-over study design but with a higher 3HHB dose (50 g of 3HHB, divided over 6 boluses of 7,8 ml). If this dose is again safe but ineffective, a third cohort of patients will be tested with the same cross-over study design with an increased dose of 75 g of 3HHB, divided over 6 doses

of 11.7ml. For each cohort of patients tested (cohort 1 to test 25 g, cohort 2 to test 50 g and cohort 3 to test 75 g), 16 patients will be included.

### Intervention Type
Supplement

### Primary outcome measure
Increase in plasma 3-hydroxybutyrate by at least 0.22 mmol/l following administration of enteral 3HHB, measured by LC-MS/MS

### Secondary outcome measures
1. Plasma levels of 3HHB and metabolites 3-hydroxybutyrate and 1,3-butanediol measured over time during (6-hour period) and after the intervention (12-hour period), measured by LC-MS/MS
2. Urine levels of 3HHB and metabolites 3-hydroxybutyrate and 1,3-butanediol over time during (6-hour period) and after the intervention (12-hour period), measured by LC-MS/MS
3. Plasma levels of cholesterol (HDL, LDL, total), triglycerides and free fatty acids over time during (6-hour period) and after the intervention (12-hour period), measured by commercial kits
4. Blood glucose concentrations during the 48 h study period, measured by blood-gas-analyzer
5. Incidence of severe (<40 mg/dl) hypoglycemia during the intervention window and until 12 h after stopping study infusion (3HHB or placebo), measured with a blood gas analyser in the ICU
6. Incidence of ketoacidosis during the intervention window and until 12 h after stopping the study infusion, measured with a ketone stick test on arterial blood in the ICU
7. Intolerance for the supplement (including abdominal discomfort or vomiting) during the intervention up until 48 hours after the last intervention, as reported by the patient or observed by the attending (study) nurse

### Overall study start date
25/01/2023

### Completion date
31/12/2026

## Eligibility

### Key inclusion criteria
1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained
2. Age >= 18 years
3. Patient expected to stay at the ICU for at least 5 days
4. The presence of a nasogastric feeding tube

### Participant type(s)
Patient

### Age group
Adult

### Lower age limit
18 Years

### Sex
Both

### Target number of participants
16 patients for each cohort, 3 cohorts maximum. Total maximum target number: 48.

### Key exclusion criteria
1. Therapy restriction code
2. Patients refusing blood transfusion upon ICU admission will be considered as having a therapy restriction upon admission and will not be included
3. Expected to die within 48 hours after screening (= moribund patients)
4. No arterial and central venous line, or expected to have one of these lines removed before the end of the study period (= not critically ill enough to be representative for the future target population).
5. Contraindication for enteral feeding
6. Readmission to the ICU after previous inclusion in the RCT
7. Inborn metabolic disease
8. Receiving ketogenic diet in ICU
9. Underweigt (BMI<20) or admitted with complications due to anorexia nervosa
10. Known to be pregnant or lactating
11. ICU admission with diabetic ketoacidosis or hyperosmolar hyperglycemic state
12. Acute or chronic liver failure
13. High glucose need to prevent spontaneous hypoglycemia
14. Metabolic acidosis (pH <7.30 and bicarbonate <18 mmol/l)

### Date of first enrolment
08/01/2024

### Date of final enrolment
01/12/2025

## Locations

### Countries of recruitment
Belgium

### Study participating centre
**UZ Leuven**
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Universitair Ziekenhuis Leuven

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**Sponsor type**
Hospital/treatment centre

**Website**
https://www.uzleuven.be/en

**ROR**
https://ror.org/0424bsv16

# Funder(s)

**Funder type**
Research council

**Funder Name**
European Research Council

**Alternative Name(s)**
ERC

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**

**Funder Name**
Vlaamse regering (Methusalem Program)

**Alternative Name(s)**
Flanders, Flemish Government, Flandre, Flandern, Vlaanderen

**Funding Body Type**

Government organisation

### Funding Body Subtype
National government

### Location
Belgium

## Results and Publications

### Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

### Intention to publish date
01/12/2027

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository (name: RDR; https://rdr.kuleuven.be/).

### IPD sharing plan summary
Stored in publicly available repository

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol file | version 1.3 | 17/04/2024 | 24/04/2024 | No | No |