Albumin catabolic rate measured by a stable isotope

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Study Design	**An open physiologic study of healthy subjects and patients with liver cirrhosis**
Karolinska Institutet **Study number**	**4-2885/2022**
Karolinska University Hospital **Study number**	**K2022-10941**
Clinicaltrials.gov number	**NCT xxxxxxxx**
Version	**1.01**
Date	**2023-07-11**

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2 SUMMARY

PROTOCOL IDENTITY AND AIM

Protocol title	Albumin catabolic rate measured by a stable isotope.
Study aim	1. Measurement of albumin catabolic rate by an oral non-radioactive tracer, D5-Phe in a group of research volunteers and a group of patients with known liver cirrhosis. Comparison of the catabolic rate between the groups, and with historical controls measured by radioiodine-labeled albumin. 2a. Evaluate how few and which measurement points are sufficient for use in clinical practice for the D5-Phe method while maintaining precision in the estimation of albumin half-life. 2b. Measurement of the fractional synthesis rate of albumin with the oral non-radioactive tracer, D5-Phe. 2c. Modeling of albumin degradation rate using oxidized albumin, i.e. two isoforms of mercaptoalbumin HNA-1 and HNA-2 and their change over time expressed as the fraction labeled with D5-Phe 2d. Correlate the amount of oxidized albumin with the albumin catabolic rate.

METHODOLOGY

Study design	Open explorative physiologic study
Primary research question	Does the albumin catabolic rate measured by the D5-Phe method differ between volunteers and patients with liver cirrhosis, and how does the catabolic rate measured by the new method compare to historical measurements with radioiodine-labeled albumin?
Effect parameters	Albumin fractional catabolic rate, albumin fractional synthesis rate, plasma albumin, changes in oxidized d5-phe-albumin over time.
Safety parameters	Vital parameters

INVESTIGATED POPULATION

Subjects	Healthy volunteers, n=12 Patients with known cirrhosis of the liver, n = 12

TIME PLAN

First subject included	September 2023
Last patient included	September 2028
Last patient completed	December 2028

3 ABBREVIATIONS

Abbreviation	Unit	Explanation
D_5-Phe		Deuterium labeled phenylalanine
ACR	mg/kg/d	Absolute catabolic rate
ASR	mg/kg/d	Absolute synthesis rate
AUC		Area under the curve of the time-concentration plot
CRF		Case Report Form
FCR	% per day	Fractional catabolic rate
FSR	% per day	Fractional synthesis rate
GCP		Good Clinical Practice
GDPR		General Data Protection Regulation
HMA		Human merkaptoalbumin (normal form, unharmed molecule)
HNA-1		Human non-merkaptoalbumin 1 (oxidized form, reversible)
HNA-2		Human non-merkaptoalbumin 2 (oxidized irreversible)
kDa	u	kilo Dalton indicated the size of a molecule
MPE	%	Mol percent excess
PV	L	Plasma volume
SEK		Swedish currency
TC		Take Care, the hospital record system

4 ADMINISTRATIVE INFORMATION

4.1 SPONSOR AND PRIMARY INVESTIGATOR

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4.3 MONITORING

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5 BACKGROUND

5.1 ALBUMIN AND PHENYLALANINE - BACKGROUND

Albumin is a medium-sized molecule, 69 kDa, and constitutes the dominant protein in plasma (40 g/liter out of a total of 70 g/liter). According to the literature, albumin is catabolized with a half-life of 14–20 days, and it is synthesized in the liver. The synthesis takes place as prealbumin whose tertiary structure is configured for export from the liver. The process from start of synthesis to export takes about 30 minutes. Albumin has several physiological functions, constitutes 70% of the oncotic pressure in plasma, functions as a transport protein and as an endogenous scavenger (binds and neutralizes free acid radicals). Lack of albumin can be acute or chronic. In acute deficiency, edema often occurs.

Low plasma albumin appears in liver disease, kidney disease, sepsis, malnutrition, and other situations. It is a predictor of shorter life expectancy and of complications associated with major surgery. Low levels can be an expression of low synthesis, as in liver disease, but in some cases, synthesis is increased despite low values in plasma, as in nephrosis or critical illness in intensive care. Measuring the turnover rate of albumin and other proteins can be of great value to better understand various diseases and their mechanisms.

Degradation of albumin is controlled to some extent from the liver, which means that patients with severe liver disease can compensate for their reduced synthesis ability by saving on the existing albumin molecules [Levitt 2016]. However, the literature is quite limited due to the difficulties associated with radioactive isotope studies, and there is a great need for new methods that can be less invasive or avoid radiation.

Phenylalanine is an essential amino acid which, due to its low free concentration in plasma and intracellularly, is particularly suitable for stable isotope studies of protein turnover. It can be labeled by deuterium, often five atoms or more, and thus different from naturally occurring phenylalanine. Phenylalanine is suitable as a tracer for measuring the degradation rate of proteins as it is found in large quantities in various proteins, can be detected with gas chromatography and mass spectrometry and has many exchangeable hydrogen atoms, which enables high analytical sensitivity. We know of only one report in the literature that used stable isotopes for endogenous labeling of proteins, but no individual proteins were assessed in the way we intend to do [Holm 2013].

5.2 ALBUMIN – MEASUREMENT OF CATABOLIC RATE

The gold standard for measurement of albumin catabolic rate is by radioiodine labeled human serum albumin.

The new idea to be evaluated in this study is to use phenylalanine (D5-Phe) orally, to measure the breakdown rate of albumin. The amino acid is incorporated into the albumin molecules during their new synthesis, and one should then achieve 4 advantages compared to the method that uses radioiodine-labeled albumin:

1) Avoiding radiation, and the costs and extensive bureaucracy that surrounds even the use of very low doses of radioactive tracers.

2) The tracer cannot detach from the albumin molecule as it forms an integral part of the amino acids in the albumin molecule.

3) It is difficult to see any influence of the labeling itself which could shorten the lifespan of the albumin molecule.

4) If this works well for albumin, then one could measure other proteins in the body with slow turnover in the same way, which would be a valuable new method.

To be able to transfer the study results to the clinic, it would be good if the number of sampling occasions could be reduced. This will be studied based on the data we receive from the group of healthy volunteers. In a second step, we will examine patients with known liver cirrhosis, but then with a much sparser sampling. Apart from day 0 when the stable isotope is ingested, we expect that 2-4 more sampling occasions may be sufficient.

5.3 ALBUMIN –MEASUREMENT OF SYNTHESIS

The synthesis rate of albumin can be calculated after intravenous administration of isotopically labeled amino acid, *i.e.* phenylalanine labeled with 5 deuterium atoms (D5-Phe). The appearance over time of labeled amino acid in newly synthesized albumin is measured [Ballmer 1990]. Estimation of the precursor pool in hepatocytes is necessary for calculation of synthesis rate. Liver biopsy in a research context is usually unacceptable because invasiveness, so therefore the "flooding dose" technique has been developed. The method is based on the idea that all pools in the body are flooded by a relatively high dose of intravenous phenylalanine so that the plasma levels thus give a reasonable figure of the precursor pool, *i.e.* the levels inside the hepatocytes.

A second idea of this study is to give an oral "flooding dose" and measure synthesis rate. The assumption that plasma levels of phenylalanine reflect the precursor pool in the hepatocytes with oral tracer has not been validated, but in this first step we want to see if we get the same steep rise of D5-Phe-albumin as with intravenous tracer and if the plasma levels of D5-Phe harmonize with a reasonable precursor pool. This part of the study is exploratory, but if the results are promising, we can proceed with validation.

At steady state, the rate of synthesis must be equal to the rate of degradation, but there are sources of error and variations over time that deserve to be elucidated and may be of great value in the planning of future studies of albumin turnover.

5.4 OXIDATION OF ALBUMIN

The albumin molecule binds to free acid radicals (scavenger function) with its sulfhydryl group in the Cys-34 position (human mercaptoalbumin HMA). During oxidative stress, the sulfhydryl group is oxidized to sulfinic acid (human non-mercaptoalbumin 1, HNA 1). This is a reversible process. Upon continued oxidation, sulfonic acid is formed, which appears to be irreversible (human non-mercaptoalbumin 2, HNA2). The result is a damaged albumin molecule that has lost its scavenger function. Oxidative stress with high levels of HNA2 may have a decisive role in the pathogenesis of severe liver failure [Oettl 2013].

There is no data in the literature regarding changes in oxidized albumin over time. We want to try to model albumin turnover by looking at how these fractions and the proportions between them change over time. We also want to see if we can reproduce previous results suggesting that the amount of oxidized albumin is higher in patients with liver cirrhosis [Oettl 2013]. Finally, we will investigate the association between albumin oxidation and albumin catabolic rate.

6 STUDY AIMS

The primary aim of the study is to compare the albumin degradation rate in healthy volunteers and in a group of patients with liver cirrhosis. We will also compare the obtained values with historical controls measured by radioiodine-labeled albumin, both in our own data from previous studies and in the literature.

The goal is partly to get a more accurate measurement, partly to get rid of the use of radioactive tracers in future metabolic studies.

There are 3 secondary objectives:

a) For the method to be clinically useful, the number of measurement points must be reduced. We will determine which measuring points could optimally be used in clinical practice to still be able to estimate the albumin degradation rate with reasonable accuracy with the peroral D5-Phe-albumin method. Of special interest is to determine the earliest time point when the tracer in the precursor pool is negligible and all albumin compartments are well stirred, *i.e.* when you can take the first sample after dosing and be sure that it is on the terminal slope. This can be examined by looking at residuals in the terminal slope of the graph that presents enrichment of D5-Phe over time. After intravenous injection of radioiodine-labeled albumin, we have previously seen that one should wait 2 weeks, but it is possible that an even longer time is needed when using D5-phenylalanine orally.

b) As a spin-off pilot study of the above, we want to see if an oral flooding dose of D5-Phe can be used to measure albumin synthesis, compared to our previous measurements with intravenous tracer. That would be a great methodological gain.

c) As a second spin-off, we will measure D5-Phe oxidized albumin and see if the rate of albumin degradation can be modeled from these early metabolites. We will also investigate the association between albumin catabolic rate and the oxidized forms of albumin.

Collected information can contribute to the optimization of future isotope studies regarding the turnover rate of albumin, so these can be conducted without the use of radioactive tracer and hopefully also give a more accurate value.

7 RESEARCH QUESTION

PRIMARY QUESTION

Is there a difference between the rate of albumin degradation as measured by D5-Phe-albumin in healthy research subjects compared to patients with liver cirrhosis? Does albumin degradation rate measured with D5-Phe albumin differ from historical controls measured with radioiodine-labeled albumin?

SECONDARY QUESTIONS

a) How few and which measurement points could be used clinically with the D5-Phe method to still obtain meaningful measurements of the albumin degradation rate?

b) Can orally administered D5-Phe be used to obtain reasonable values of albumin fractional synthesis rate compared to historical controls as measured by intravenous administration of the same tracer in our previous studies?

c) Can measurement of different forms of oxidized d5-Phe-albumin over time be used to model the rate of albumin degradation?

d) Does the rate of albumin degradation correlate with the amount of oxidized albumin?

8 ENDPOINTS

FCR measured by D_5-Phe-albumin, FSR measured by D_5-Phe-albumin, P-albumin, HNA-1, HNA-2.

9 STUDY DESIGN

This study is an open, exploratory pilot study in two stages. In step 1, healthy volunteers are examined. On day 0, an oral dose of phenylalanine 45 mg per kilogram of body weight 50% MPE D5-phenylalanine is given, and repeated blood samples are taken over 120 minutes to measure FSR. Plasma volume will be calculated anthropometrically.

Afterwards, the research subjects return for single venipunctures around days 7, 14, 21, 28, 42, 56, 70 and 84 to measure D5-Phe-albumin, P-albumin, and labeled and unlabeled oxidized forms of albumin (human non-mercaptoalbumin), HNA 1 and HNA- 2, respectively.

After analysis of the collected data, phase 2 of the study begins with patients who have cirrhosis of the liver. The procedure is identical to the above except that the sampling after day 0 takes place on fewer occasions, tentatively at 3, 8 and 12 weeks, but the protocol may be slightly adjusted based on the results from the healthy research subjects.

10 STUDY PROCEDURES

10.1 INFORMED CONSENT

The research subjects are informed orally and in writing about the study and the study-specific procedures by the principal researcher, another researcher or research nurse. After that, written consent is obtained. They then undergo a simple health examination and routine blood samples are taken.

A researcher evaluates inclusion and exclusion criteria, so that there is no contraindication to participating in the study. Here, record is kept in the existing record system (Take Care) that the research person participates in a clinical study in accordance with the Patient Data Act and the regulations of the National Board of Health and Welfare.

10.2 DAY 0. MEASUREMENT OF FRACTIONAL SYNTHESIS RATE

In the morning, the research subject arrives fasting at the research department at Perioperative Medicine and Intensive Care, Huddinge. Pregnancy tests are taken on female research subjects of childbearing age, 40–55 years. A peripheral venous line is placed for repeated blood sampling. Two grams of D5-Phe is taken per os as a suspension. Blood samples are taken at 0, 10, 20, 30, 50, 70, 90, and 120 minutes for measurement of FSR, that is D5-Phe and D5-Phe-albumin. Actual sampling times are documented in the CRF.

The oxidized forms of albumin will also be measured in some of these samples.

Blood samples for determination of P-albumin, B-Hb and B-hematocrit are taken for determination by routine lab. Actual sampling times are documented in the CRF.

10.3 DAY 7, 14, 21, 28, 42, 56, 70, AND 84. MEASUREMENT OF FRACTIONAL CATABOLIC RATE.

The healthy volunteers come back on 8 occasions for venous sampling of P-albumin, D5-Phe-albumin, and the oxidized forms of albumin as absolute values and the ratio between labeled and unlabeled fractions. Sampling occasions are documented in the CRF. Exact dates and times are documented but may differ from those in the headline.

Patients with liver cirrhosis only come back on preliminary 3 occasions, after approximately 21, 56 and 84 days.

11 METHODS AND ANALYSIS

11.1 MEASUREMENT METHODS

Quantitative measurement of enrichment of isotopically labeled phenylalanine is done using gas chromatography-mass spectrometry at the Karolinska Stable Isotope Core where Olav Rooyackers is the laboratory director. Quantification of total phenylalanine (the precursor) is performed by mass spectrometry against an internal standard. Oxidized forms of albumin will be measured by high performance liquid chromatography.

11.2 SAMPLE HANDLING

The samples for the measurement of stable isotopes will be labeled in a de-identified way and stored in the existing biobank at the Anesthesia and Intensive Care Clinic Karolinska University Hospital Huddinge at minus 80ºC while waiting for the material collection to be completed and then analyzed in the same analysis round to obtain the best possible precision in accordance with local routines. Åke Norberg is the responsible part for the sample collection. All sample material will be destroyed once the study is published. The code key is kept in a locked room in the anesthesia department, internal address K32, at Karolinska University Hospital, Huddinge.

12 SUBJECTS

Due to the many return visits, the healthy research subjects will be recruited through advertising within the staff at Karolinska University Hospital Huddinge. The short visits for blood sampling can then take place in connection with the employees' work shifts.

Liver cirrhosis patients will be recruited from the Clinic of Hepatology, ME Upper Abdomen, Karolinska University Hospital, Huddinge.

12.1 INCLUSION CRITERIA, HEALTHY VOLUNTEERS

- Healthy volunteers, females and males, ≥ 40 years old
- Good peripheral blood vessels
- Signed written consent.

12.2 INCLUSION CRITERIA, PATIENTS WITH LIVER CIRRHOSIS

- Adult patients with known compensated liver cirrhosis and radiological or endoscopic signs of portal hypertension, such as varices, splenomegaly, or shunts.
- Signed written consent.

12.3 EXCLUSION CRITERIA

- Planned surgical procedure within 3 months (due to possible blood loss *i.e.* loss of tracer)
- Pregnancy at dosing
- Phenylketonuria
- Participating in other study with stable isotopes within 60 days.
- Circumstance that causes the responsible researcher to assess the research person's participation as inappropriate.

13 CRITERIA FOR DISCONTINUATION

13.1 PATIENT RELATED CRITERIA

The research subject can at any time cancel his participation in the study without giving a reason. If possible, the researcher/nurse can write the reason for the end of the study in the CRF.

- Acute serious illness in research subjects
- Decompensated liver failure with bleeding or ascites drainage
- The research person chooses to cancel his participation.

13.2 INVESTIGATOR'S CRITERIA AND EVALUABILITY

The principal investigator can decide that the research subject cannot continue in the study. This can be caused by lack of evaluability or other reasons detailed below:

- Technical failure of equipment
- Personnel reasons that make safe and standardized method analysis impossible

This must be stated in the CRF with the date and time.

13.3 SUBJECT LOG

The investigator will keep a record of all subjects who have been asked about participation and research subjects who have been on screening visits in a log list. The log list is kept in the investigator's

folder which is available at the department of Perioperative Medicine and Intensive Care. It shows all screened subjects, included and not included.

14 ASSESSMENT OF SAFETY AND EFFICACY

Phenylalanine is an essential amino acid found naturally in various proteins in food and in all commercial enteral nutrition solutions. Deuterium is a stable isotope of hydrogen that occurs naturally in 0.015% of all water molecules: The risk with oral intake of phenylalanine 45 mg per kilogram of body weight 50% MPE D5-phenylalanine is considered negligible.

The research subjects are monitored at the Research Department at the Unit for Perioperative Medicine and Intensive Care, Karolinska University Hospital Huddinge, by staff who are well acquainted with emergency events. Monitoring of the research subject's heart rate, ECG, respiratory rate, saturation (oximetry), blood pressure and temperature is done before and during the first 120 min after oral administration of stable isotope on day 0 in accordance with the research unit's routines.

Laboratory samples are analyzed at the ISO-certified Karolinska University Laboratory, Huddinge.

15 STATISTICS AND DATA MAMAGEMENT

15.1 DATA MANAGEMENT

For the research subjects, the form from the health check will be de-identified and attached to the CRF. Monitoring curve day 0 is attached to the CRF. Otherwise, data is retrieved from the hospital electronic records (Take Care, TC) and placed decoded in the CRF.

All data concerning the endpoints will be put into a database that will be locked when the data collection is complete. De-identified and coded demographic and study data will be compiled and entered in an electronic database.

15.2 STATISTICAL ANALYSIS

Demographic data such as age, height, weight, BMI, gender, and routine lab, will be presented as number, mean and standard deviation, or median and range depending on the nature of the data. The liver cirrhosis patients will furthermore be presented with diagnosis and existing measures of liver disease severity in TC, such as the Child-Pugh score and the Model for End-stage Liver Disease.

Plasma half-lives of D5-Phe-albumin will be calculated from the assumed log-linear decline over time, the terminal slope λz, and analyze of residuals will be performed to determine when the terminal slope is reached. The groups will be compared by t-test or Mann-Whitney U-test depending on the appearance of the data. We will also do non-compartmental analysis of the data.

All values of FCR and FSR will be included in a planned joint pharmacokinetic analysis later in the study program.

15.3 DETERMINATION OF THE NUMBER OF SUBJECTS

No previous measurements of albumin degradation rate measured with D5-Phe are available in the literature.

With radioiodine-labeled albumin there are measurements showing that the FCR for volunteers is 9.6 ± 1.5% per day, against 6.9 ± 1.9 for cirrhotic patients [Hasch 1967]. With these numbers corresponding to an effect size of 1.56, we would reach 80% power with 8 people in each group, two-sided test and a significance level of 5%. However, these measurements were made on inpatients, and it is possible that outpatient cirrhosis patients at Huddinge, who are expected to be stable in their liver failure for 3 months, are somewhat less impaired in their liver function, *i.e.* that the difference between the groups is somewhat smaller.

If we look at our own data on synthesis measurements with the flooding-dose technique for volunteers [Dumitrescu 2018] and liver disease patients [Amouzandeh 2023 submitted manuscript], we have FSR values of 12.8 ± 2.3% per day respectively 6.1 ± 3 ,2. At steady state, fractional synthesis rate is equal to fractional degradation rate and then 5 people in each group would be enough to reach 80% power to detect this difference with a two-tailed test and a significance level of 5%.

Overall, we think that with 12 people in each group, we can withstand 2 dropouts per group and still be reasonably confident of having a good power. The risk of dropouts is affected by the long observation period, 12 weeks. With 10 observations in each group, you reach 80% power to find an effect size of 1.35 with a two-sided test and a significance level of 5%.

16 ACCESS TO SOURCE DATA

The principal investigator is responsible for ensuring that the patient record manager at the clinic establishes a confidentiality relationship with the monitor and other independent reviewer (*i.e.* auditor) who is given permission to verify the data in the patient record. For this, written consent is required from the research subject.

17 QUALITY CONTROL

17.1 MONITORERING

The investigator and staff must set aside time for monitoring. The principal investigator is responsible for monitoring being done by an independent monitor with knowledge of GCP, to ensure that the study is conducted according to GCP, GDPR and according to the study protocol. The sponsor has contracted the Clinical Research Unit KFE at Perioperative Medicine and Intensive Care, Karolinska Solna for monitoring this study.

18 ETHICS

The principal investigator is responsible for the application for approval from the ethics review authority. The study will be conducted according to the study protocol, GCP, GDPR and the Declaration of Helsinki.

19 DATA MAMAGEMENT AND ARCHIVE

19.1 CASE REPORT FORMS

The data collected in the study will be registered in so-called Case Report Forms (CRF) where the research person or patient is only identified with a code number and initials. The code key is stored in such a way that unauthorized persons cannot access it. De-identified and coded copies of lab lists, patient record entries and diagnoses (Take Care) and monitoring records will also be included in the CRF. Data collected in the study in the CRF will be transferred to a database that the principal investigator is responsible for.

19.2 ARCHIVE

Study documents will be filed for at least 10 years. The documents shall be filed in readable stated for future audit or inspection by authorities.

20 FINANCIAL SUPPORT AND INSURANCE

The study is funded by research grants. The research subjects are insured by the patient injury insurance.

Healthy volunteers will receive grants for loss of income, in total 2000 SEK, for only the first day 1000 SEK. Patients with liver cirrhosis will get 400 SEK per visit for travel expenses.

21 PUBLICATION OF RESULTS

The intention is to publish the results in a scientific journal, together with previously unpublished data from one of our previous radioiodine studies of albumin kinetics.

22 REFERENCES

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23 SIGNATURE

Huddinge 2023-07-04

Åke Norberg, Associate Professor, Sponsor, and Principal Investigator