Endogenous Glucose Production in Subjects with Glycogen Storage Disease Type Ia estimated by a single oral dose of stable isotopes: an investigator-initiated human pilot study.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inborn errors of metabolism
Study type	Observational invasive

Summary

ID

NL-OMON50039

Source
ToetsingOnline

Brief title
ENGLUPRO GSDIa: Endogenous glucose production in GSDIa

Condition

- Inborn errors of metabolism

Synonym
Glycogen Storage Disease Type Ia (GSDIa) & Von Gierke's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Een sponsorverzoek voor een deel van de salariskosten van Dr. A. Rossi is gehonoreerd door Associazione Italiana Glicogenosi (Italiaanse GSD patientenvereniging).,Een sponsorverzoek voor uitvoering van de studie is goedgekeurd door Ultragenyx Pharmaceutical Inc. Het contract wordt momenteel opgesteld door juristen van UMCG en Ultragenyx. Het bedrijf stelt geen inhoudelijke voorwaarden of beperkingen aan de opzet van de studie of aan de publicatie.

Intervention

Keyword: glucose, stable isotope

Outcome measures

Primary outcome

The main study parameter is the EGP quantification assessed by measurement of

blood D-[6,6-2H2]glucose enrichment.

Secondary outcome

Secondary study parameters are glucose area under the curve, glucose clearance

rate, glucose bioavailability, glucose apparent volume of distribution and CGM

data.

Study description

Background summary

Glycogen storage disease type I (GSDI) is characterised by severe fasting intolerance, associated with hypoketotic hypoglycaemia, accumulation of glycogen and fat in the liver and kidneys, causing hepatomegaly and renomegaly. Two major subtypes are recognized: GSDIa, due to glucose 6-phosphatase defect (G6PC gene variants) and GSDIb due to defect of glucose 6-phosphate transporter (SLC37A4 gene variants). Large phenotypic variability is observed within GSDIa patients with respect to clinical picture, biochemical parameters and dietary response.

Notably, GSDIa patients retain a limited capacity for endogenous glucose

production (EGP). Despite several mechanisms for residual EGP have been proposed, the origin of residual EGP in GSDIa patients is unknown. Data from G6PC-deficient hepatocytes suggest that either increased glycogen debranching or lysosomal glycogen breakdown accounts for residual EGP in GSDIa.

Medically prescribed diets are the cornerstone of management, but novel, innovative treatments are promising, such as AAV8-mediated gene therapy and mRNA therapy. Therefore, longitudinal monitoring of outcomes after therapeutic interventions in GSDIa patients becomes warranted, for which nowadays (1) assessment of microsomal glucose-6-phosphatase activities ex vivo (necessitating invasive liver biopsies) and (2) execution of (invasive, clinical) fasting challenges in vivo are available.

Theoretically, less-invasive monitoring may include the application of (3) stable isotope methods to quantify EGP, and (4) advanced continuous glucose monitoring (CGM) in the home situation, but proper studies are lacking.

Study objective

The primary objective is to test the feasibility of EGP quantification in adult GSDIa patients by stable isotopes after a single oral D-[6,6-2H2]glucose dose.

Secondary objectives are to compare EGP assessed by a single oral D-[6,6-2H2]glucose dose (a) in GSDIa patients versus matched healthy participants, (b) in severe versus attenuated GSDIa patients, (c) in the pre-prandial state versus the fed state in GSDIa patients, (d) in the pre-prandial state versus the fed state in healthy participants, (e) in the controlled hospital setting versus the at home setting in GSDIa patients, (f) in the controlled hospital setting versus the at home setting in healthy participants.

In addition, we will compare the CGM data from GSDIa patients versus matched healthy participants.

Study design

An investigator-initiated human pilot-study.

Study burden and risks

The trial is considered to be a low-risk study.

For the healthy participants there is no benefit in this study. By careful history taking we aim to reduce the risk of including patients with diabetes or fasting intolerance.

The sites* clinical research team at the UMCG has previously performed stable isotopes oral loads in healthy volunteers and has a longstanding tradition in supervised controlled clinical dynamic tests in patients with inborn errors of metabolism, and GSD in particular. To minimize the impact on quality of life and discomfort due to hospitalization and sample collections, two experiments will be conducted under controlled circumstances during a short hospital stay (<24 hours) and one experiment will take place at home.

The stable isotope that will be used is safe, normally metabolised and without any expected adverse effects; the dose of the stable isotope is relatively low and does not affect metabolism either.

The blood tests will be conducted on capillary blood obtained by fingerstick (or fingerprick) and collected on filter paper as dried blood spots (DBS), before analysis. CGM will be performed throughout the study, which will increase safety for GSDIa patients.

For GSDIa patients, the results of this study may develop into methods to quantify glucose metabolism in a relative non-invasive mode, to assess outcomes after novel, innovative treatments, such as AAV8-mediated gene therapy and mRNA therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, The GSDIa patients must meet all of the following criteria:
• The diagnosis should be confirmed by G6PC mutation analysis
• Age above 16 years
• Stable medical condition before the start of the test procedures

Exclusion criteria

A potential GSD Ia patient who meets any of the following criteria will be excluded from participation in this study:
• Age < 16 years
• Recent (< 1 month) history of hospitalization due to hypoglycaemia
• Intercurrent illness, defined as (a combination of) decreased dietary intake, vomiting, diarrhoea and fever (>38.5*C) in the week prior to the visit
• Pregnancy

A potential age and gender-matched healthy participant who meets any of the following criteria will be excluded from participation in this study:
• Confirmed diagnosis or history suggestive of diabetes mellitus
• First grade family member with a confirmed diagnosis associated with fasting intolerance
• History suggestive of fasting intolerance

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-01-2021
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	28-09-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04311307
CCMO	NL73191.042.20