Hepatic triglyceride biosynthesis in humans with different insulin resistance phenotypes

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To determine the effects of tissue-specific (adipose tissue or muscle) vs global (combined) IR on hepatic triglyceride biosynthesis in humans. To determine differential effects of an acute exercise intervention on hepatic triglyceride biosynthesis...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON53815

Source
ToetsingOnline

Brief title
TRISYNTH

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Dyslipidemia; insulin resistance

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Yale University (o.b.v. een NIH-beurs op naam van collaborator Dr. D. Vatner)

Intervention

Keyword: Heterogeneity, Insulin resistance, Lipogenesis

Outcome measures

Primary outcome

Difference in %DNL between subjects with global vs muscle-only insulin

resistance as well as the differential effects of premeal exercise on %DNL in

these groups.

Secondary outcome

Associations between plasma markers, metabolites, and increased lipogenesis in

humans with insulin resistance.

Study description

Background summary

The promises of precision medicine will be realized with a better understanding of the heterogeneous physiological phenotypes that underpin common disease states, such as insulin resistance (IR) and dyslipidemia. We posit that IR is not a single entity, but the manifestation of discrete tissue-specific pathologies. For example, we have found that among equally obese patients, some have global insulin sensitivity, some demonstrate tissue-specific (skeletal muscle) IR only, and others have global IR. This diversity in IR likely impacts the pathogenesis of dyslipidemia, thereby explaining some of the variability in the clinical response to existing lipid-lowering medications (e.g., fibrates). A better understanding of this heterogeneity may reveal novel therapeutic targets and help clinicians to provide better precision medicine for patients with different subtypes of IR.

Study objective

To determine the effects of tissue-specific (adipose tissue or muscle) vs global (combined) IR on hepatic triglyceride biosynthesis in humans. To determine differential effects of an acute exercise intervention on hepatic triglyceride biosynthesis in these groups.

Study design

Observational study with cross-sectional design.

Study burden and risks

Subjects will visit the metabolic unit on 4 occasions (screening, an oral glucose tolerance test, DNL measurement without and with premeal exercise). A glucose drink will be used to assess whole-body glucose metabolism and insulin sensitivity. Stable isotope-labelled water (deuterium) will be used to assess %DNL into hepatic VLDL. Stable isotopes behave like their natural substrate (water) and have been previously used without serious adverse effects when infused or ingested. Overall, the risks associated with participation (pain from venous blood sampling, nausea from glucose drink) are minimal. We believe that the scientific value of our study will outweigh the burden and risks associated with participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Ability to give informed consent; - Age 18-65y; - Overweight or class 1 obesity, defined as BMI 25-35 kg/m2; - Modest hypertriglyceridemia, defined as fasting plasma triglycerides 1.3-3.0mM; - High risk of insulin resistance, defined as fasting plasma insulin >64pM; - Stable weight for at least 3mo prior to participation.

Exclusion criteria

- Active or chronic liver disease, kidney disease, congestive heart failure, unstable angina, history of acute cardiovascular events within 6mo of screening, history of seizures or syncope, or an active infection requiring antimicrobial therapy; - Use of insulin, thiazolidinediones, GLP1 agonists, SGLT2 inhibitors, or sulfonylureas; - Use of fibrates, omega 3 (fish oil), niacin, or PCSK9 antagonists; - Use of systemic glucocorticoids within 60d prior to participation; - Hematocrit <35%; - Pregnancy of breastfeeding; - Active tobacco use, excessive alcohol intake (>14U/wk), or history of drug abuse.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-11-2023
Enrollment:	110
Type:	Actual

Ethics review

Approved WMO Date:	14-09-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL83166.018.22