Glucose metabolism in Familial Hypobetalipoproteinemia

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29272

Source
NTR

Brief title
FHBL

Health condition

patients with familial hypobetalipoproteinemia and matched controls

Sponsors and support

Primary sponsor: -
Source(s) of monetary or material Support: Department of Endocronology & Metabolism, AMC, Amsterdam

Intervention

Outcome measures

Primary outcome

To determine in detail:

1) Quantity of liver- and muscle triglycerides

2) Body fat distribution

3) hepatic insulin sensitivity

4) peripheral insulin sensitivity

5) intramyocellular differences regarding fatty acid handling
of drug-free subjects with FHBL as compared to healthy controls matched for age, sex, body mass index, waist circumference and physical activity.

Secondary outcome

Adiponectin levels and levels of different adiponectin forms in plasma.

Study description

Background summary

Subjects with familial hypobetalipoproteinemia (FHBL) are characterized by low plasma total cholesterol, LDL cholesterol and total apolipoprotein B. Moreover, the prevalence of nonalcoholic fatty livers (steatosis) is increased in these subjects. Hepatic steatosis is associated with hepatic and peripheral insulin resistance and has been suggested to play a role in the pathogenesis of diabetes mellitus type 2 and the metabolic syndrome. Due to the hepatic steatosis in subjects with FHBL, hepatic glucose production could be increased. As peripheral insulin sensitivity is correlated to hepatic insulin sensitivity (in part probably by a common mechanism, namely increased availability and intracellular concentrations of longchain fatty acids and their metabolites and in part by a yet largely unknown direct influence from the liver on peripheral glucose uptake), one could expect peripheral insulin resistance as well. However subjects with FHBL have normal glucose and insulin level
s as well as normal oral glucose tolerance tests (OGTT).
Two hypotheses can be formulated to explain these findings:
A] The existence of increased in stead of decreased peripheral insulin sensitivity. This could be explained by a lower concentration of IMCL (probably a surrogate marker for increased fatty acid metabolites intracellularly) in muscle of subjects with FHBL as they have a dysfunctional triglycerides transport system.
B] Increased plasma adiponectin. Adiponectin is produced and secreted by adipose tissue and has an insulin sensitizing effect on glucose metabolism and enhances fatty acid oxidation (which would promote a lower IMCL concentration). In animal experiments, administration of adiponectin stimulated glucose-uptake in muscles and suppressed hepatic glucose output. High levels of adiponectin could counteract the effects of hepatic steatosis on insulin sensitivity in subjects with FHBL.
We, therefore, propose a detailed and controlled study of carbohydrate and lipid metabolism in subjects with FHBL and their matched controls, using stable isotopes, combined with measurements of liver and intramyocellular fat content.

Study objective

We hypothesize that:

1. Subjects with FHBL have disturbed glucose metabolism, consisting of decreased hepatic insulin sensitivity leading to increased glucose production but increased peripheral insulin sensitivity due to decreased concentrations of IMCL and free fatty acid metabolites.

2. Adiponectin plasma levels are increased due to increased production/ secretion or reduced clearance to compensate for the enhanced glucose production.

Intervention

Subjects will be studied on 2 occasions:

- after an overnight fast glucose production, disposal and oxidation will be measured using [6,6-2H2]glucose and indirect calorimetry. Lipolysis will be measured using [2H5]glycerol. Muscle metabolites will be measured via muscle biopsy. Subjects will be studied at basal and during a two step hyperinsulinemic euglycemic clamp.

- Hepatic and muscle lipid content will be measured by 1HMRS (magnetic resonance spectroscopy).

Total and regional fat mass will be measured by a DEXA-scan, subcutaneous and visceral fat will be measured by a single slice CT-scan.

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Eligibility criteria

Inclusion criteria

1. Subjects with documented FHBL, who have liver steatosis (FHBL group).
Healthy subjects (control group), exactly matched for age, sex, body mass index, waist circumference and physical activity

2. Male subjects

3. Age > 18 years

4. Body Mass Index 20-35 kg/m2

5. No participation in other medical intervention studies in the last three months

6. Able to communicate well with the investigator and to comply with the requirements of the study

7. Written informed consent.

Exclusion criteria

1. Known any somatic illness, including neoplasm, metabolic or endocrine disorder, neurologic disorder, active infection, or recent surgical procedures within 3 months of study initiation.

2. Use of medication, which can influence glucose or FFA metabolism (insuline, anabolic steroids, growth hormone, testosteron, DHEA, statines, ACE-inhibitors, AII-antagonists, aspirin)

3. Presence of FHBL linked to chromosome 3p21 (since they have no liver steatosis)

4. History of recreational drug use within the last 30 days, or regular consumption of greater than three units of alcohol per day

5. Diabetes mellitus

6. Seropositive for HbsAg, HbcAg, HCV, HAV or HIV

7. Having a pacemaker or other metal device in the body

8. Claustrophobia

9. Regular exercise above sedentary level.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2008
Enrollment:	16
Type:	Anticipated

Ethics review

Positive opinion

Date:	29-10-2008
Application type:	First submission

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
NTR-new	NL1449
NTR-old	NTR1510
Other	: 05/223
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results
N/A