Glucose metabolism in Familial Hypobetalipoproteinemia

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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...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON29272

Bron NTR

Verkorte titel FHBL

Aandoening

patients with familial hypobetalipoproteinemia and matched controls

Ondersteuning

Primaire sponsor: -Overige ondersteuning: Department of Endocronology & Metabolism, AMC, Amsterdam

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To determine in detail:
1) Quantity of liver- and muscle triglycerides

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- 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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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.

Onderzoeksproduct en/of interventie

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.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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, All-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.

Onderzoeksopzet

Opzet

Туре:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland	
Status:	Werving gestart
(Verwachte) startdatum:	01-11-2008
Aantal proefpersonen:	16
Туре:	Verwachte startdatum

Ethische beoordeling

Positief advies	
Datum:	29-10-2008
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1449
NTR-old	NTR1510
Ander register	: 05/223
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten

N/A