Insulin resistance in Dutch males of Hindostanian origin vs. Dutch males of Caucasian origin.

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People of South-Asian/Indian descent, such as the Hindostani population in The Hague, develop DM2 at a much younger age and lower BMI as compared to Caucasian controls of the same age and BMI. Moreover, the incidence and seriousness of...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON25420

Bron
Nationaal Trial Register

Aandoening

diabetes mellitus type 2
insulin resistance
insulineresistentie
cardiovascular disease
cardiovasculaire aandoening
hart- en vaataandoening
ectopic fat accumulation
ectopische vetophoping
mitochondrial dysfunction
mitochdonriële dysfunctie

Ondersteuning

Primaire sponsor: Leiden University Medical Center
Overige ondersteuning: Roba

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Difference in all of the following study endpoints between Caucasians and Hindostani at baseline and after a dietary intervention; HFHC in the young group and VLCD in the middle-aged men:
1. Whole body glucose disposal determined by [6,6-2H2] glucose infusion and a two-step hyperinsulinaemic euglycaemic clamp;
2. EGP determined by [6,6-2H2] glucose infusion and a two-step hyperinsulinaemic euglycaemic clamp;
3. Glucose and lipid oxidation as determined by indirect calorimetry;
4. Body fat distribution: Hepatic and myocardial triglyceride content, visceral/subcutaneous abdominal fat and cardiac function, assessed by MRI/MRS;
5. Insulin signalling pathway in skeletal muscle and adipose tissue as assessed by expression and activation of IRS1-associated PI3K, PKB, AS160, GLUT4;
6. mTOR nutrient sensing pathway in skeletal muscle: mTOR, S6K1, PRAS40, raptor;
7. Muscle and adipose tissue mitochondrial function (mRNA levels of PGC-1á, mitochondrial enzymes, including the complexes of the electron transport chain/oxidative phosphorylation, uncoupling protein 3 [UCP3], mitochondrial copy number, and activity of mitochondrial enzymes (citrate synthase and cytochrome C oxidase));
8. Intramyocellular lipid content (Oil-red-O staining) and ceramide, acyl-co-enzyme A and triacylglycerol, and diacylglycerol levels;
9. Pancreatic function (first and second phase insulin response) as assessed by OGTT (only measured before the intervention);
10. Adipocyte function before the intervention: Plasma FFA’s, resistin, adiponectin, leptin, inflammatory mediators;
11. Calorie intake and daily activities as determined by a 3-day diary.

Toelichting onderzoek

Achtergrond van het onderzoek

This study investigates why Hindostani compared to Caucasian people develop type 2 diabetes and cardiovascular diseases at a younger age and lower BMI. The cause of thse differences is unkonw but might be related to body fat distribution and/or fatty acid handling. South Asians have a much smaller subcutaneous fat depot and relatively more visceral fat compared to Caucasians. Visceral fat is presumed to be more deleterious. Impaired fatty acid beta-oxidation in muscle and/or adipose tissue mitochondria might be the cause of ectopic fat storage. The resulting excess intermediates of fatty acid metabolism will accumulate in the cells and disturb metabolic processes (e.g. the insulin signaling pathway and insulin

secretion). The mTOR pathway is a modulator of both insulin sensitivity and mitochondrial function. We hypothesize that changes in the activity of mTOR between Hindostani and Caucasian in skeletal muscle and adipose tissue biopsies, may underly/contribute to skeletal muscle insulin sensitivity and/or even mitochondrial function.

We will investigate healthy young males with a normal BMI and healthy middle-aged males with abdominal adiposity. Both groups will be studied before and after a diet. The young group after a high-fat-high-calorie-diet; and the middle-aged group after a very-low-calorie-diet.
Measurements which will be done are: hyperinsulinemic, euglycemic clamp; muscle biopsies; fat biopsies; indirect calorimetry; MRI/MRS, anthropometric measurements and blood samples.

Doel van het onderzoek

People of South-Asian/Indian descent, such as the Hindostani population in The Hague, develop DM2 at a much younger age and lower BMI as compared to Caucasian controls of the same age and BMI. Moreover, the incidence and seriousness of cardiovascular disease is much higher in Hindostani compared to Caucasians.
The susceptibility to DM2 and atherogenic diseases of South-Asians might be causally related to body fat distribution and/or fatty acid handling. Impaired fatty acid beta-oxidation in muscle and/or adipose tissue mitochondria might be the cause of ectopic fat storage in, for example, skeletal muscle. The resulting excess intermediates of fatty acid metabolism will accumulate in the cells and disturb metabolic processes and thus organ function.

Recent studies have identified the nutrient- and energy-sensing mammalian target of rapamycin (mTOR) pathway as modulator of both insulin sensitivity and mitochondrial function.

We hypothesize that changes in the activity of mTOR between Hindostani and Caucians in skeletal muscle and adipose tissue biopsies, before and after high-fat-high-calorie-feeding (HFHC) or calorie-restriction (CR), may underly/contribute to skeletal muscle insulin sensitivity and/or even mitochondrial function. This could then lead to ectopic lipid accumulation with subsequent organi-specific dysfunction.

CR improves carbohydrate metabolism, while a HFHC-diet induces carbohydrate intolerance in high risk subjects. Because mTOR is a nutrient-sensing pathway it is likely we hypothesize that, if a dysfunction in this pathway underlies the early development of DM2 in Hindostani, the diets (HFHC and CR) will elicit different responses in the Hindostani as compared to the Caucasians.

Onderzoeksopzet

N/A

Onderzoeksproduct en/of interventie

High-fat-high-calorie-diet (HFHC) (young group):

Consisting of a subject's normal diet plus 375 cc cream per day, providing 150% of energy demands and consisting of 50% fat. Duration of HFHC diet: 5 days.

Very-low-calorie-diet (VLCD) (middle-aged group):

Consisting of 3 sachets of Modifast per day, providing approximately 450 kcal/day. Duration of VLCD diet: 8 days.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

We will study:

1. Young, healthy male Caucasians and Hindostani before and after 5 days of high-fat-high-calorie diet on the one hand, and;

2.Middle-aged male Caucasians and Hindostani with abdominal adiposity before and after 8 days of caloric restriction on the other hand.

Young men:

1. Male healthy volunteers, 12 Hindostani and 12 Caucasians, born in the Netherlands;

2. Age >= 18 years and <= 25 years;

3. BMI >= 19 and <= 25;

4. 1 parent or grandparent with DM2 and >= relative.

Middle-aged men:

1. Male volunteers, 12 Hindostani and 12 Caucasians, born in the Netherlands;

2. Age 40 - 50 years;

3. Waist circumference > 94 cm for Caucasians and > 90 cm for Hindostani;

4. BMI >= 25 and <= 30;

5. 1 parent or grandparent with DM2 and >= 1 other relative.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Diabetes mellitus as defined by ADA criteria;

2. Any significant chronic disease;

3. Renal, hepatic or endocrine disease;

4. Clinical cardiovascular disease, including complaints of angina pectoris or intermittent claudication;

5. Smoking;

6. Use of medication known to influence glucose and/or lipid metabolism;

7. Recent weight changes or attemps to lose weight (> 3 kg weight gain or loss, within the last 3 months);

8. Difficulties to insert an intravenous catheter;

9. Severe claustrophobia;

10. Contra-indications for MRI;

11. Recent blood donation (within the last 3 months);

12. Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-02-2010
Aantal proefpersonen:	48
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	13-08-2010
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	NL2366
NTR-old	NTR2473
Ander register	METC LUMC : P09-143
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A