Betacel dysfunction induced by impaired pancreas anatomy and insulin sensitivity in subjects with heterozygous EXT1 or EXT2 Mutations

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Assessment of glucose homeostasis and pancreas size (MRI) in 10 subjects with heterozygous mutations in EXT-1, in 10 subjects with heterozygous mutations in EXT-2 and 10 unaffected related controls as well as 10 subjects with known type 2 diabetes...

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

Summary

ID

NL-OMON38131

Source
ToetsingOnline

Brief title
BEEM-2

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Diabetes, EXT-1, EXT-2, pancreas MRI

Outcome measures

Primary outcome

-pancreas size (MRI)

Secondary outcome

- pancreas permeability (MRI)

Study description

Background summary

A recent Genome Wide Association Study (GWAS) identified novel risk loci for type 2 diabetes including EXT-2. This gene codes for exostosin, which is an enzyme involved in the elongation of heparan sulfate, a glycosaminoglycan present throughout the human body. Patients with EXT-1 and EXT-2 mutations are characterized by the hereditary multiple exostoses/ multiple osteochondromas (HME/MO) syndrome, an autosomal dominant syndrome causing multiple benign epiphysial bone tumors during (pre-) puberty due to 50% reduction in heparan sulfate synthesis. However, mice with these mutations are also characterized by insulin secretion problems as well as a smaller size of the pancreas. We therefore performed hyperglycaemic normoinsulinemic clamps in these HME/MO patients and found that these subjects are characterized by impaired insulin secretion and 50% reduction in betacell capacity compared to unaffected related controls (BEEM study, MEC 08/262). Elaborating on these findings, we now would like to investigate whether human subjects with these mutations are also characterized by smaller pancreas size (assessed by MRI), which could cast new light on the causes of type 2 diabetes mellitus.

Study objective

Assessment of glucose homeostasis and pancreas size (MRI) in 10 subjects with heterozygous mutations in EXT-1, in 10 subjects with heterozygous mutations in EXT-2 and 10 unaffected related controls as well as 10 subjects with known type 2 diabetes mellitus.

Study design

Case control study

Study burden and risks

This study does not have specific advantages for the study subjects. The results of this observational study may help researchers understanding the role of heparan sulfates in the development of type 2 diabetes mellitus. Subjects will be asked to fast during 12 hours. This is not considered to be harmfull. A total amount of 30 ml blood wil be collected, this is not considered to be harmfull. MRI pancreas imaging is a non-invasive technique (no radiation) which takes about 30 minutes. We will use gadolinium as an intravenous contrast agent which could potentially be harmful in subject with renal dysfunction. We will therefore screen renal function by measuring plasma creatine before MRI and subjects with renal dysfunction will be excluded from participation. We believe the information gathered from this study outweighs the burden of these interventions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Caucasian subjects (male/female), aged between 18-65 years of age with heterozygous EXT-1 or EXT-2 mutations as well as unaffected related controls matched for age and gender and subjects wiht known type 2 diabetes mellitus.

Exclusion criteria

claustrophobia, pregnant subjects or female participant at childbearing age not using adequate anticonception, renal dysfunction during screening, exogenous insulin use.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-05-2012
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	26-01-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2012
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	NL35744.018.11