The effect of Glucocorticoid Receptor Polymorphisms and Metabolically Active Genetic Variants on Glucose Metabolism in the Skeletal Muscle

Published: 19-10-2012
Last updated: 26-04-2024

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

Summary

ID

NL-OMON47510

Source
ToetsingOnline

Brief title
GR polymorphisms, metabolic genetic variants and insulin resistance

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, insulin resistance

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Glucocorticoid receptor polymorphism, Glucose Metabolism, Insulin Resistance, Skeletal Muscle

Outcome measures

Primary outcome

New study outcome parameter:

- profile of GC-polymorphisms

- genetic variants influencing energy-metabolism

Study outcome parameters (already obtained):

-Body composition (underwater weighing)

-Insulin sensitivity (hyperinsulinemic-euglycemic clamp)

-Substrate oxidation (indirect calometry during the clamp)

-Skeletal muscle oxidative capacity

-VO2max-test

-Skeletal muscle lipid accumulation in muscle biopsies.

Secondary outcome

NA

Study description

Background summary

Glucocorticoids (GCs) such as the stress hormone cortisol are produced in the adrenal glands. In order to exert their effects in the human body, they need to be bound to the glucocorticoid receptor (GR), which makes the GR an essential factor in mediating cortisol effects. GC's are well known for thier effects in the human body such as anti-inflammatory and immunosuppressive actions, and their effects on glucose and protein metabolism. The efficacy of GCs and the prevalence as well as the severity of side effects are highly variable between individuals whereas sensitivity to GCs in the same patient seems to be rather stable, suggesting genetic factors to play a role in GR sensitivity.

Recently it was found that a polymorphism (= genetic variation) in the GC gene (more specifically BclI) is associated with an increased response to GCs, hereby confirming the hypothesis that the BclI indeed is a functional polymorphism.

In follow up of this finding, we tested patients of the big a combined cohort study (CODAM and Hoorn Studies) and found that homozygous carriers of the BclI polymorphisms have increased total body fatness and insulin resistance. This finding is of major importance because it might (partly) explain why some patients might be more susceptible to weight gain and the development of insulin resistance, ultimately leading to type 2 diabetes. Understanding the underlying mechanisms through which this polymorphism might act to induce these effects can contribute to a better understanding, treatment and prevention of type 2 diabetes. Unfortunately, at present, the exact mechanism through which the BclI polymorphism leads to hypersensitivity of the GR and its subsequent metabolic and body compositional effects remains poorly understood.

The group of Prof. Schrauwen has performed a variety of studies, investigating the effects of ectopic lipid accumulation in several organs (in obesity and type 2 diabetes) and the relationship with the development of insulin resistance. Doing so, the glucose and fat metabolism in the skeletal muscle of these subjects has been quite well characterised. Furthermore so, biopsy material and plasma samples are available from these studies for further research.

Genotyping subjects (both obese and type 2 diabetic subjects) from these studies for GR polymorphisms and other genetic variants influencing energy-metabolism would provide an excellent opportunity to investigate the effects of these polymorphisms on substrate metabolism in the skeletal muscle in a minimally invasive manner since no new human tissue has to be obtained and all measurements have already been performed. It only requires a new blood sample for genetic determination.

At the time of inclusion, almost all subjects have given their consent that their tissue may be used for further research in line with the initial research and that they can be approached for additional research.

Study objective

The major objective is to investigate the effects of the GR polymorphisms on metabolism in the skeletal muscle, in order to unravel the pathophysiological mechanisms underlying previously observed clinical effects in carriers of this polymorphisms. This will be done by investigating the following (already obtained) parameters:
-Body composition (underwater weighing)
-Insulin sensitivity (hyperinsulinemic-euglycemic clamp)
-Substrate oxidation (indirect calometry during the clamp)
-Skeletal muscle oxidative capacity
-VO2max-test
-Skeletal muscle lipid accumulation in muscle biopsies.

Blood plasma samples will be obtained to genotype each subject for the GR polymorphisms and other genetic variants influencing energy metabolism.

Study design

In this observational study, all subjects enrolled will be approached and asked to give one blood sample (if DNA is not already available) in which genotyping for the GR polymorphisms and genetic variants influencing energy-metabolism can be performed. Subjects will be divided per genotype the above mentioned parameters will be compared among the different genotypes of the GR polymorphisms.

Study burden and risks

Combining the four studies, provides an excellent opportunity to investigate the effects of these polymorphisms on glucose and protein metabolism in the skeletal muscle in a minimally invasive manner since no new human tissue has to be obtained and all measurements have already been performed. Only one vial of blood from each subject needs to be obtained.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects selected from studies 09-3-033; 07-3-028; 04-257; 03-015; 06-3-038; 09-3-039; 11-3-092; 11-2-003; 13-3-058; 13-2-030; 15-3-030; 113003; 153046; 163019; 163052; 173008; 173017; 173021; 173024; 173031; 173037; 183001 and 183006 (n=447).

Exclusion criteria

NA, these already have been set by the previous studies.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-07-2014
Enrollment:	447
Type:	Actual

Ethics review

Approved WMO Date:	19-10-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-02-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-12-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL41486.068.12