Sitagliptin prophylaxis for glucocorticoid-induced impairment of glucose metabolism and beta-cell function in males with the metabolic syndrome-X: a randomized, placebo controlled, double blind, 2x2 factorial designed intervention trial.

Published: 14-11-2008
Last updated: 06-05-2024

The objective of this study is to assess whether sitagliptin may prevent prednisolone-induced impairment of glucose metabolism and beta-cell function.

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

Summary

ID

NL-OMON35611

Source
ToetsingOnline

Brief title
SPHINX study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Therapeutic and nontherapeutic effects (excl toxicity)

Synonym
Adverse effects of prednisolone; glucocorticoid-induced beta-cell dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: EFSD grant,Merck Sharp & Dohme (MSD)

Intervention

Keyword: Beta cell dysfunction, DPP-4 inhibitor, Glucocorticoids, Metabolic syndrome

Outcome measures

Primary outcome

To compare the effect of sitagliptin 100 mg daily versus placebo, given simultaneously with prednisolone 30 mg daily during 2 weeks, on glucocorticoid-induced glucometabolic abnormalities (measured as area-under the curve of postprandial glucose during a standardized mixed-meal test) in males with the metabolic syndrome.

Secondary outcome

To compare the effect of sitagliptin 100 mg daily versus placebo, given simultaneously with prednisolone 30 mg daily during 2 weeks, on glucocorticoid-induced beta-cell dysfunction in males with the metabolic syndrome.

Various measures of beta-cell function will be used, including:

o First-phase insulin secretion during a hyperglycemic clamp test

o Second-phase insulin secretion during a hyperglycemic clamp test

o Arginine-induced insulin secretion during a hyperglycemic clamp test

o Model-derived parameters of beta-cell function derived from a mixed-meal test

Exploratory objectives:

A: To compare the effects of sitagliptin versus placebo given simultaneously with prednisolone during 2 weeks in males with the metabolic syndrome with respect to:

- Insulin sensitivity
- Incretin secretion during standardized meal tests
- The plasma levels of additional biomarkers such as lipoproteins, adipo(cyto)kines, and markers of systemic inflammation, both in the fasting and postprandial state
- Body composition and body fat distribution
- mRNA and protein expression of genes involved in glucose and lipid metabolism in subcutaneous adipose tissue and/or skeletal muscle
- Blood pressure
- Microvascular function

B: To compare the effect of a four-week treatment with sitagliptin, versus placebo in males with the metabolic syndrome on:

- Time to normalization of glucose metabolism after cessation of the two-week prednisolone treatment
- Liver fat content

C: To compare the effect of a two-week treatment with prednisolone 30 mg daily, on the under A summarized parameters, relative to placebo in males with the

metabolic syndrome.

Study description

Background summary

Glucocorticoids (GCs) are the most frequently prescribed anti-inflammatory and immunosuppressive drugs, with proven efficacy in a wide range of (auto-immune) disorders. Unfortunately, GC therapy is also associated with numerous side effects, including osteoporosis, gastric ulcers, hypertension and dysmetabolic changes, which in a large number of patients lead to glucose intolerance and diabetes. Interestingly, in clinical practice, drugs are routinely prescribed to prevent GC-induced osteoporosis and gastric ulcers, however, to date no measures are being undertaken to prevent the development of diabetes. GCs are well known to reduce insulin sensitivity, both after acute and chronic exposure. In the last decade however, research on the diabetogenic effects of GCs has become more focused on the role of impaired insulin secretion and beta-cell dysfunction. GCs acutely inhibit insulin release in vitro, but also increased insulin secretion in vivo, most likely to compensate for insulin resistance. Rodents and humans with pre-existent compromised glucose metabolism, showed impaired insulin secretion after GC treatment. In a pilot study in healthy males, GCs significantly interfered with various aspects of beta-cell function, as assessed by modelling analysis of glucose and insulin concentrations during mixed-meal tests, a method that has been developed in recent years. In particular, the potentiation factor which encompasses various potentiating signals to the beta-cell (e.g. glucose-induced potentiation, non-glucose stimuli, incretins, neural factors) was markedly impaired. These data suggest that the harmful effects of GCs on beta-cell function are not as yet fully detailed and that the complete spectrum of these actions may only become unveiled when using a more physiological approach, in particular by addressing the role of the intestinal-islet axis.
Based on these preliminary findings, we hypothesized that, inasmuch as GCs interfere with various aspects of the relation between nutrient stimuli and insulin secretion, the novel modality to treat T2DM, i.e. DPP-4 inhibitors such as sitagliptin, which potentially restore this relation by enhancing incretin activity, may particularly be effective in reducing GC-induced deleterious effects on the beta-cell in males with the metabolic syndrome.

Study objective

The objective of this study is to assess whether sitagliptin may prevent prednisolone-induced impairment of glucose metabolism and beta-cell function.

Study design

The SPHINX study is a randomized, placebo-controlled, double-blind, 2x2 factorial-designed intervention trial.
It concerns a monocenter studie (VUmc, Amsterdam) and a total of 60 participants will be included.

Intervention

Subjects will be randomized to one of four groups, to receive either I) prednisolone 30 mg and sitagliptin 100 mg daily; II) prednisolone 30 mg and sitagliptin-placebo daily; III) prednisolone-placebo and sitagliptin 100 mg daily; IV) prednisolone-placebo and sitagliptin-placebo daily. Prednisolone/prednisolone-placebo will be administered for 14 days and sitagliptin/sitagliptin-placebo for 28 days.

Study burden and risks

We are well aware of the possible demand that may be imposed on the participants. Overall, participants will travel 7 times to the study location. The duration of these visits ranges between 30 minutes and 7 hours, with a total of 34,5 hours. A total amount of 500 mL blood will be withdrawn. The maximum amount of blood to be collected during one visit is 120 mL.
All possible measures will be taken to minimize the discomfort for the participants. During the clamps and meal tests, patients will assume a semirecumbent position, to alleviate discomfort, and will be allowed to read or watch TV/video. Following the tests, all participants will be presented with a meal and coffee/tea. During the clamps (a restricted regimen of) water intake is allowed. Subjects with claustrophobia are excluded from MRI-scans. Lidocaine will be used as a local anaesthetic during the biopsy procedures. Ice packages will be used to reduce the development of a hematoma. Our current experience indicates that participants tolerate these muscle and adipose tissue biopsies very well. Sitagliptin is tolerated very well by it's users. Only mild side effects such as nasopharyngitis and headache occur in a small percentage of users. Since prednisolone has been used extensively, its potential, clinically relevant side-effects are well documented. Aside from the development of transient impairment of insulin sensitivity and beta-cell dysfunction, we do not expect to find other adverse effects in our short treatment period with medium-doses of prednisolone. In a recent study in healthy males, using an identical intervention as in our study, it was shown that GC-induced insulin resistance was quickly resolved after cessation of therapy. Glucose levels were not changed during the study, and the increased levels of C-peptide and pro-insulin (signs of insulin resistance) had returned to baseline after one-week of follow-up. Furthermore, no participants had to discontinue the study due to health problems, and no serious adverse events were reported (refer to protocol page 16-18).

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelaan 1117
1081 HV Amsterdam
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelaan 1117
1081 HV Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. signed informed consent
2. caucasian male
3. normal day-and night rythm
4. metabolic syndrome (according to IDF criteria):
Waist > 93 cm and at least 3 of the following criteria:
- triglycerides > 1.7 mmol/L
- HDL cholesterol < 1.03 mmol/L
- blood pressure > 130/85 mmHg
- disturbed glucose tolerance (definded as: fasting plasma glucose above 5.6 mmol/L, but no diabetes [see exclusion criteria]).

Exclusion criteria

1. allergy for prednisolone
2. any other contra-indication for prednisolone use.
3. use of glucocorticoids in the past 3 months
4. Recent participation in a clinical trial
5. Blood donation in the past 3 months
6. (history of) alcohol or drugs abuse.
7. Not willing or able to sign the informed consent or not being able to understand the study information
8. serious (pulmonary, liver, kidney) diseases
9. history of cardiovascular disease (such as MI or CVA)
10. psychiatric disorder
11. depression
12. any condition that interferes with the HPA axis
13. malignancy
14. diabetes mellitus (defined as FPG * 7.0 mmol/l and/or 2hPG * 11.1 mmol/l)
15. other condition or usage of medication that may interfere with study endpoints of hypothesis. Eligibility will be assessed in each individual case by the research physician and internist.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-02-2009
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Januvia
Generic name:	Sitagliptin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prednisolone
Generic name:	Prednisolone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-11-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2011
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
EudraCT	EUCTR2008-004985-25-NL
ClinicalTrials.gov	NCT00721552
CCMO	NL25430.029.08