The effects of metformin on immune function.

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Ethical review	Approved WMO
Status	Pending
Health condition type	Mycobacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON41133

Source
ToetsingOnline

Brief title
Metformin Trial

Condition

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

Synonym
immunometabolism; effect of metabolism on immunity

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: EU FP7/2007-2013; grant agreement No. 305279

Intervention

Keyword: immune, metformin, system, tuberculosis

Outcome measures

Primary outcome

The primary objective of the study is to evaluate the effects of orally administered metformin on the immune responses of stimulated peripheral blood mononuclear cells (PBMC*s) and macrophages from healthy individuals. The effects of metformin will be determined by measuring the ex-vivo responsiveness of leukocytes to various pathogens and inflammatory stimuli. The primary outcome of this measure is production of cytokines (for example TNF-α, IL-6, IL-10, IL-1β, IL-17, IL-22, IFN-γ secretion by ex vivo stimulated PBMCs.

Secondary outcome

• Gene expression and transcriptional analysis of samples with a strong focus on immunity, inflammation, epigenetic and metabolic related pathways.

• Epigenetic modulation of gene and protein expression by metformin

• Metabolic regulation of key energy sensors (AMPK, mTOR, AKT, PKA etc) by metformin

Study description

Background summary

Metformin is the most widely administered type 2 diabetes mellitus drug (T2DM). It reduces plasma glucose levels by decreasing hepatic gluconeogenesis and increasing muscular intake of glucose. Metformin has a well established safety record with few adverse effects and decades of research that have elucidated its cellular effects on glycaemic control and glucose metabolism. Nevertheless metformin*s effects on the immune system are largely unknown. To date only one

study has shown that short term exposure of peritoneal macrophages and bone marrow derived DCs to metformin result in reduced MHC antigen presentation capacity.

Nonetheless recent data emerging from epidemiological studies show that patients with diabetes have a 3 fold increased risk to MTB. Our in-vitro data indicate that metformin may negatively affect We therefore wondered if the intake of metformin had a significant effect on the immune responses of healthy individuals to ex-vivo stimulations that include MTB.

Study objective

The primary objective of the study is to evaluate the effects of orally administered metformin on the immune and metabolic responses of stimulated peripheral blood mononuclear cells (PBMC*s) and macrophages from healthy individuals.

Study design

Healthy volunteers who meet all inclusion criteria, none of the exclusion criteria, pass the screening and have given informed consent to participate in the study will be included in this trial. The subjects will take metformin based on the following regime for a total of 6 days.

Day 1: 1 x 500 mg (dinner)
Day 2: 1 x 500 mg (breakfast) & 1 x 500 mg (dinner)
Day 3: 1 x 500 mg (breakfast) & 1 x 500 mg (dinner)
Day 4: 1 x 500 mg (breakfast) & 2 x 500 mg (dinner) & phonecall
Day 5: 2 x 500 mg (breakfast) & 2 x 500 mg (dinner)
Day 6: 2 x 500 mg (breakfast)

On the day of screening, day -1, 0, day 5, day 8 and day 19 of the trial, subjects will be asked to come to the research room of the internal medicine department for blood sampling (see 3. Study design, p.11 for flowchart). During screening we will determine BMI, kidney function (creatinine levels), HBA1c, insulin, glucose, uric acid levels and lipid profiles to exclude persons with kidney dysfunction and/or metabolic disorders like diabetes mellitus type 2, familial hypercholesterolemia, gout etc.
On days -1 and 0 we would like to determine (1) basal level of cytokine production of PBMCs and macrophages in response to various stimuli. After 1 day, 3 days and 14 days of metformin ingestion we will perform the same experiments to determine the effects of metformin on these measurements. The 3 day and 14 day timepoints will assess the long term immunological effects of metformin.

Study burden and risks

There is no direct benefit to the participating subjects but it is expected that these results will potentially lead to a better understanding of the long-term effects of an extensively used drug. The risk of adverse effects is minimized by choosing a healthy study population at the age of 18 - 45 years. 12 healthy volunteers will take the aforementioned (see Intervention) regimen for a duration of 6 days in total. All volunteers will donate 8 tubes of blood at 4 different time points and 10 mL of blood during screening. The risk involving local hematoma formation at the site of the blood drawing will be minimized through blood collection by experienced persons. The risk of lactic acidosis is minimal (3 cases per 100,000 patient-year); moreover a recent study published in the Cochrane Database, investigated data from 247 recent clinical studies and found no cases of lactic acidosis among participants who were assigned to take metformin1.

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

healthy, > 18 years of age, no history of TB, no history of cardiac or renal disease

Exclusion criteria

DM in first degree relatives, obesity (BMI > 25), use of medication

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2014
Enrollment:	12
Type:	Anticipated

Ethics review

Approved WMO

Date:	29-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL47793.091.14