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The effects of metformin on vascular function and adipocyte AMP-activated protein kinase (AMPK) activation in type 2 diabetes

Submission date 19/06/2010	**Recruitment status** No longer recruiting
Registration date 29/06/2010	**Overall study status** Completed
Last Edited 11/10/2011	**Condition category** Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
03MT024

Study information

Scientific Title
The effects of metformin on vascular function and adipocyte AMP-activated protein kinase (AMPK) activation in type 2 diabetes: a randomised, double blind, glycaemia-controlled crossover trial

Study objectives
Epidemiological studies have suggested that overweight type 2 diabetic patients may have fewer cardiovascular events on metformin compared with sulphonylureas. The mechanisms of metformin action have yet to be fully elucidated, although recent data have implicated AMP-kinase activation as a potential mediator of metformin action in hepatocytes and skeletal myocytes. We propose to take this a step further. We will conduct a double-blind randomised glycaemia-controlled crossover study in 20 overweight type 2 diabetic patients comparing interventions of metformin with a sulphonylurea. In this group we will study resistance artery endothelial function ex vivo, based on the hypothesis that metformin will augment NO-dependent vasorelaxation. In addition, we will quantify AMPK activity in fat cell lysates from the same patients to clarify whether metformin regulates this kinase in adipocytes. Together, these data will increase our understanding of metformin's vascular action and may pave the way for novel therapeutic targeting of AMPK in the context of metabolic and vascular pathophysiology.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North Glasgow University Hospitals NHS Trust Ethics Committee approved on the 20th January 2004 (ref: 03/154/2)

Study design
Single centre randomised double blind controlled crossover trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Type 2 diabetes

Interventions

The study was single-centre and had a randomised, double blind, glycaemia-controlled crossover design. After full explanation of experimental procedures aided by a subject information sheet, written informed consent was obtained. Each subject was issued with details of the study as well as the investigators' contact telephone numbers. Patients on monotherapy discontinued medication during a six-week run-in period. After this period, patients were randomised to receive metformin (500 mg three times daily) or gliclazide (80 mg twice daily with a lunchtime placebo capsule to ensure blinding) for ten weeks, aiming for a similar reduction in HbA1c. Each drug had a two week dose titration as follows:
Week 1: Gliclazide 80 mg once daily with breakfast, metformin 500 mg once daily with breakfast
Week 2: Gliclazide 80 mg once daily with breakfast and dummy capsule at lunch, metformin 500 mg twice daily with breakfast and lunch
Weeks 3 - 10: Gliclazide 80 mg twice daily at breakfast and evening meal and dummy capsule at lunch, metformin 500 mg three times daily with breakfast, lunch and evening meal

Subjects were asked to inform the investigators of any medication started or discontinued during the study period. No specific advice on lifestyle was given at the time of randomisation.

Study randomisation:
Randomisation and tablet supply was co-ordinated by the hospital pharmacy. Metformin and gliclazide capsules of identical appearance were manufactured by the pharmac. A computerised randomisation list was made. Randomisation codes were put into sealed envelopes and stored by the pharmacist. Medication bottles were numbered, and allocation was done in sequence. Unblinding was performed at the end of the study period.

Subject visits:
The study required subjects to attend the Clinical Investigation and Research Unit, University of Glasgow on a total of nine occasions:
Week 0 - Screening visit
Week 1 - Start of phase 1
Week 5 - Interim visit
Week 10 - End of phase 1 (with biopsy)
Week 12 - Stitch removal
Week 16 - Start of phase 2
Week 21 - Interim visit
Week 26 - End of phase 2 (with biopsy)
Week 28 - Stitch removal

Patients were contacted by telephone at two weeks and attended the CIRU for a brief assessment at five weeks during each phase to check on any side effects and to assess glycaemic control. Any patient with significant osmotic symptoms or a fasting blood glucose of greater than 15 mM would have been withdrawn from the study. Patients were then required to attend the CIRU at 08:30 hours at the end of the ten week study phase having fasted from midnight (and having abstained from alcohol, caffeine and moderate/heavy exercise in the preceding 72 hours) for clinical measures, adipose biopsy and blood sampling for biochemical analysis. Taxis were available to transfer volunteers to and from the CIRU. Snacks were provided at the CIRU when the study protocol was completed. Following a six-week washout phase, the groups were crossed over.

Intervention Type

Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Metformin, gliclazide

Primary outcome measure
Measured at the end of each 10-week study phase:
1. Body mass index
2. Blood pressure
3. Analysis of routine blood samples (fasting venous blood samples for urea, creatinine, electrolytes, total cholesterol, triglycerides, high density lipoprotein [HDL]-cholesterol, loew density lipoprotein [LDL]-cholesterol, glucose, liver function tests and HbA1C)
4. Analysis of non-routine blood samples (total adiponectin, tumour necrotising factor-alpha [TNF-a], interleukin-6 [IL-6] and asymmetric dimethyl-arginine [ADMA])
5. Pulse wave velocity (PWV)
6. Wire myography
7. Adipose AMPK activity assays

Secondary outcome measures
No secondary outcome measures

Overall study start date
09/03/2004

Completion date
09/03/2006

Eligibility

Key inclusion criteria
1. Body mass index (BMI) range 27 - 40 kg/m2
2. HbA1c greater than 7% but less than 11% (Diabetes Control and Complications Trial [DCCT]) at screening
3. Previously treated with diet alone or oral monotherapy (i.e., metformin or sulphonylurea). Subjects on monotherapy had discontinued medication during the six-week run-in period.
4. Males, aged between 50 - 70 years

Participant type(s)
Patient

Age group
Adult

Sex
Male

Target number of participants
20 men with type 2 diabetes

Key exclusion criteria
1. Subjects on warfarin treatment
2. Subjects treated with insulin currently or in the previous 12 months
3. Previous intolerance of metformin or sulphonylurea
4. Presence of contra-indication to metformin therapy for example renal disease or congestive cardiac failure
5. Cardiovascular event (i.e., electrocardiogram (ECG)/troponin proven myocardial infarction [MI] or cerebrovascular accident [CVA]) in previous 6 months

Date of first enrolment
09/03/2004

Date of final enrolment
09/03/2006

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
Division of Cardiovascular and Medical Sciences
Glasgow
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G12 8QQ

Sponsor information

Organisation
Greater Glasgow Health Board (North Glasgow University Hospitals Division) (UK)

Sponsor details
300 Balgray Hill Road
Glasgow
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G12 3UR

Sponsor type
Hospital/treatment centre

Website
http://www.nhsggc.org.uk

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (BHF) (UK) (ref: PG/03/114/16038)

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2011		Yes	No