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Adolescent type 1 diabetes cardio-renal intervention trial

Submission date
30/07/2007

Recruitment status
No longer recruiting

Registration date
03/10/2007

Overall study status
Completed

Last Edited
21/02/2022

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Type 1 diabetes mellitus (T1DM) is a lifelong condition where a person is unable to prevent their blood sugar (glucose) levels from becoming too high. When a person is suffering from TD1M, the body is unable to produce a hormone called insulin, which is responsible for breaking down glucose and turning it into energy. The only effective way of treating T1DM is by regularly injecting the insulin that the body is unable to produce. It is very important that sufferers take their insulin regularly, as otherwise it can lead to serious complications, such as damage to the heart and blood vessels (cardiovascular system) and kidneys (renal system). The risk of these complications seems to be higher in people diagnosed early in life, during childhood and adolescence when compared to people diagnosed during adulthood. The Adolescent type 1 diabetes cardio-renal intervention study (AdDIT) is a study aiming to evaluate drugs acting on blood pressure (ACE inhibitors) and lipid (fat) levels (statins) in adolescents with T1DM at risk of developing cardiovascular and renal complications. The AdDIT follow up study aims to look at the long term risk of developing these complications in adolescents who took part in the AdDIT study.

Who can participate?
Adolescents aged 10-16 who have type 1 diabetes and are at risk of developing cardiovascular or kidney disease.

What does the study involve?
In the AdDIT study, participants are randomly allocated to one of four groups who receive different drugs for 2-4 years. Those in the first group receive a statin (cholesterol-lowering drug) and placebo (dummy drug), those in the second receive a statin and an ACE inhibitor (blood pressure-lowering drug), those in the third group receive an ACE inhibitor and a placebo, and those in the fourth group receive two placebos. For all participants, at the start of the study and then yearly until the end, samples are taken to measure for signs of kidney or cardiovascular disease.
In the AdDIT follow up study, participants from the AdDIT study are followed up for a further five years in order to find out whether the drugs used are able to protect against development of cardiovascular kidney disease in the long-term.

What are the possible benefits and risks of participating?
There are no direct benefits for AdDIT participants, but the study results will help in the future in improving the management of type 1 diabetes in young people with type 1 diabetes. During the AdDIt trial period study participants mayexperience some of the sides effects associated with statins or ACE inhibitors, but close monitoring will reduce risk of any relevant risk. There are no notable benefits or risks associated with the AdDIt follow up study.

Where is the study run from?
1. University of Cambridge Addenbrookes Hospital (UK)
2. Hospital for Children, Perth (Australia)
3. The Hospital for Sick Children, Totonto (Canada)

When is the study starting and how long is it expected to run for?
August 2008 to November 2016 (AdDIT)
August 2016 to March 2022 (AdDIT follow up)

Who is funding the study?
1. Diabetes UK (UK)
2. Juvenile Diabetes Research Foundation (UK)
3. British Heart Foundation (UK)

Who is the main contact?
1. Professor David Dunger (AdDIT)
2. Ms Rowena Weighell (AdDIT follow up)

Contact information

Type(s)
Scientific

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Prof David Dunger

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Type(s)
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Additional identifiers

Protocol serial number
RP06

Study information

Scientific Title
Adolescent type 1 diabetes cardio-renal intervention trial

Acronym
Adolescent Diabetes Intervention Trial (AdDIT)

Study objectives
AdDIT:
To determine whether intervention with Angiotensin Converting Enzyme Inhibitors (ACEI), statins, or a combination of both, when compared with placebo, will:
1. Reduce albumin excretion as assessed by six monthly measurement of Albumin/Creatinine Ratio (ACR) in three early morning urines
2. Reduce the incidence of Microalbuminuria (MA) (ACR log mean greater than 3.5 mg/mmol (males) or greater than 4 mg/mmol [females] in two out of three urines) at the end of the study period
3. Reduce the incidence of MA during the six month run out period following the completion of intervention phase

AdDIT follow up:
The primary study outcomes will be to assess, at the end of the 5-year follow-up period the prevalence of vascular complications. Specifically:
1. The prevalence of Micro/macroalbuminuria
2. The prevalence of retinopathy
3. The prevalence of decline in renal function
4. The prevalence of early signs of macrovascular disease, as assessed by PWV, cIMT, FMD

Ethics approval required
Old ethics approval format

Ethics approval(s)
AdDIT: South West Research Ethics Committee, 06/03/2008, ref: 08/HO206/4
AdDIT follow up: East of England - Cambridge South Research Ethics Committee, 20/04/2016, ref: 16/EE/0053

Study design
AdDIT:
Randomised controlled double blind clinical trial

AdDIT follow up:
Multi-centre multi-national longitudinal observational study

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Diabetic nephropathy and cardiovascular disease

Interventions
AdDIT:
Eligible subjects who have provided informed consent and have completed baseline assessments are randomized using a secure internet-based service (www.sealedenvelope.com). This provides randomization with minimization. Subjects are allocated to one of the four treatment regimens after minimizing differences between arms on the following baseline characteristics: HbA1c (<7.5, 7.5-8.5, > 8.5%), log mean standardized ACR (>1.2 to <1.7, >1.7), gender, age (11-13, >13 years), duration of disease (<5 years, >5 years), total cholesterol (≥ 4.46 or < 4.46 mmol/l).

Four treatment groups:
1) Statin-placebo
2) Statin-ACE inhibitor
3) Ace inhibitor-placebo
4) Placebo-placebo

Statin: Atorvastatin at a single dose of 10 mg daily for oral administration with an identically labeled placebo
ACE inhibitor: Quinapril available at 2 doses: 5 mg and 10 mg with appropriately matched placebo. Subjects are started on 5 mg and reviewed after two weeks; if there have been no adverse reactions in this time, the dose is increased to 10 mg daily, otherwise it will maintained at 5 mg. Any subjects experiencing apparent side effects (postural hypotension or persistent cough) have the option of changing to the lower dose at any point during the study.

Drug exposure and trial duration: 2-4 years

AdDIT follow up:
The AdDIT follow up study will be a 5-year observational study, starting from the completion of the AdDIT trial. It will consist of 5 annual study visits and phone or email contact by the study team every 6 months.
Baseline visit:
1. Consent and/or assent
2. Assessments of height, weight, waist circumference, blood pressure and collection of information about smoking status and medical history.
3. Blood sample collection to be used for investigations including: DNA extraction (epigenetic

studies) where not previously collected (AdDIT Final visit or at Run-out, Intervention study), centralised measurement of HbA1c, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, lipoproteins, CVD (hsCRP, ADMA) and renal (creatinine, SDMA, Cystatin C) markers, new biomarkers through explanatory studies of proteomics/metabolomics, microRNAs
4. 3 early morning urine samples (ACR, microRNA, proteomics/ metabolomics).

12-monthly study visits with:
1. Assessments of height, weight, waist circumference, blood pressure and collection of information about smoking status and medical history.
2. Blood sample collection to be used for investigations including: centralised measurement of HbA1c, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, lipoproteins, CVD (hsCRP, ADMA) and renal (creatinine, SDMA, Cystatin C) markers
3. 3 early morning urine samples (ACR, microRNA, proteomics/ metabolomics).

6-monthly contact
All Follow Up recruits will be contacted every 6 months between annual visits either by phone or email, depending on individual preference, to collect information on clinical events, glycaemic control and medications, and to ensure contact details are kept up to date.

Final visit
The final assessment will take place after 5 years of follow up.
1. Assessments of height, weight, waist circumference, blood pressure and collection of information about smoking status and medical history.
2. Blood sample collection to be used for investigations including: centralised measurement of HbA1c, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, lipoproteins, CVD (hsCRP, ADMA) and renal (creatinine, SDMA, Cystatin C) markers, new biomarkers through explanatory studies of proteomics/metabolomics, microRNAs and epigenetic changes recently implicated in vascular complications
3. Cardiovascular assessments: Assessments will include measurement of Carotid artery intima-media thickness (cIMT), and where facilities are available, Pulse Wave Velocity (PWV) and Endothelial Pulse Amplitude Tonometry (EndoPAT).
4. Retinal photographs taken during routine care will also be collected. Anonymised digital copies of the retinal photographs will be used for centralised grading of diabetic retinopathy and, where possible, also for detailed study of the retinal microvasculature.
5. Neuropathy assessment: The development of neuropathy will be assessed through the monitoring of clinical signs and symptoms.

Long-term follow-up
A longer term follow-up of the AdDIT cohort is planned through NHS systems analysis (UK) and other similar strategies in Australia and Canada

Original interventions:
Four arm randomisation:
1. Quinapril, 5 - 10 mg daily and placebo
2. Atorvostatin, 10 mg daily and placebo
3. Quinapril and atorvostatin
4. Placebo

The duration of study will be three to four years, that is until subjects reach the age of 14 to 18 years and they will also be studied for an additional six months during the run out period.

Intervention Type

Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Quinapril, atorvostatin

Primary outcome(s)
AdDIT:
The primary endpoint is defined as the area under the curve over time of log albumin-creatinine ratio per year, with standardisation for gender, age and duration of disease.

AdDIT follow up:
Prevalence of vascular complications at the end of the 5 year follow-up period, specifically:
1. The prevalence of Micro/macroalbuminuria, as assessed by urinary albumin creatinine ratio (ACR)
2. The prevalence of retinopathy, as assessed by retinal imaging
3. The prevalence of decline in renal function, as assessed by markers such as cystatin C, SDMA, creatinine-based glomerular filtration rate
4. The prevalence of early signs of macrovascular disease, as assessed by direct vascular measures, such as PWV, cIMT, FMD

Key secondary outcome(s))
AdDIT:
1. Changes in carotid intimal media thickness, between baseline and the end of intervention period
2. Changes in arterial Blood Pressure (BP), lipids and other lipoproteins, CVD risk markers (high-sensitive C-Reactive Protein [hsCRP] and Asymmetric Dimethylarginine [ADMA]), assessed every six months during the intervention period
3. Changes in measures of Glomerular Filtration Rate (GFR) (plasma Symmetrical Dimethylarginine [SDMA], creatinine and cystatin C) assessed every six months during the intervention period
4. Changes in quality of life and health economics

AdDIT follow up:
Tracking of ACR, lipid levels, blood pressure, abnormal inflammatory markers during the 5-year follow up period, based on yearly assessments.

Completion date
01/03/2022

Eligibility

Key inclusion criteria
AdDIT:
1. Type 1 diabetes diagnosed for greater than one year
2. Aged 11 to 15 years
3. High risk for the development of diabetic nephropathy and Cardiovascular Disease (CVD) as predicted by albumin excretion in the upper tertile after appropriate adjustment for age, sex, age at diagnosis and duration of disease

AdDIT follow-up:
1. Participants of the AdDIT Intervention and non-intervention cohort
2. Have given written informed consent to participate
3. Have completed involvement in the AdDIT study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
11 years

Upper age limit
15 years

Sex
All

Key exclusion criteria
AdDIT:
1. Non-type 1 diabetes, i.e., type 2 diabetes, insulin dependent diabetes related to monogenic disease, secondary diabetes
2. ACR based on six early morning urines deemed to be at low risk for subsequent development of CVD or diabetic nephropathy
3. Pregnancy, or unwillingness to comply with contraceptive advice and regular pregnancy testing throughout the trial
4. Severe hyperlipidaemia and family history data to support diagnosis of familial hypercholesterolaemia
5. Established hypertension unrelated to diabetic nephropathy
6. Prior exposure to the investigational products, statins and ACEI

AdDIT follow-up:
1. Inability to give consent
2. Any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to make the patient ineligible for inclusion because of safety concern

Date of first enrolment
01/08/2008

Date of final enrolment
31/12/2012

Locations

Countries of recruitment
United Kingdom

England

Australia

Canada

Study participating centre
University of Cambridge Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
University of Cambridge and Cambridge University Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Charity

Funder Name
Diabetes UK

Alternative Name(s)
The British Diabetic Association, DIABETES UK LIMITED, British Diabetic Association

Funding Body Type
Private sector organisation

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

Location

United Kingdom

Funder Name
Juvenile Diabetes Research Foundation

Alternative Name(s)
Juvenile Diabetes Research Foundation Ltd, JUVENILE DIABETES RESEARCH FOUNDATION LIMITED, JDRF UK, JDRF

Funding Body Type
Government organisation

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

Location
United Kingdom

Funder Name
British Heart Foundation

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

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Results article	results	01/12/2014		Yes	No
Results article	protocol	21/02/2022	21/02/2022	Yes	No
Protocol article		17/12/2009		Yes	No
HRA research summary			26/07/2023	No	No