

Lawson Clinical Research Services

Victoria Hospital
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Canada

Letter of Information

Title: Reduction of Adolescent Risk Factors for Type 2 Diabetes and Diabetes-related Cardiovascular Disease (REACH)

Sponsor: Children's Hospital, London Health Sciences Centre
Lawson Health Research Institute
University of Western Ontario

Investigators: Dr. Cheril Clarson, Dr. Stewart Harris,
Dr. Michelle Jackman, Dr. Farid Mahmud
Dr. Harry Prapavessis, Dr. Kevin Shoemaker
Justine Wilson

The pronouns 'you' and 'your' should be read as referring to the participant rather than the parent or guardian who is signing the consent form for the participant.

Introduction

You are being invited to voluntarily participate in a clinical research study because you are between the ages of 10 and 16 years and may be at risk for developing diabetes or atherosclerosis (hardening of the arteries) in the future. The purpose of this letter is to provide you with the information you require to make an informed decision on participating in this study. Please take your time to read the following information carefully. If you need further information, please ask your study doctor.

Study Purpose

The purpose of this study is to compare changes in lifestyle with diet and exercise alone to changes in lifestyle with diet and exercise in combination with metformin medication. Metformin is a pill that makes the body's insulin work better and when used in combination with improvements in diet and exercise can promote weight loss.

Background

The risk for type 2 diabetes and diabetes related heart disease starts in childhood. Rates of obesity and type 2 diabetes are increasing in children and teenagers and obesity increases the risk for future development of type 2 diabetes and heart disease. It is known that both lifestyle changes and metformin medication can prevent development of diabetes in adults who are at risk for developing diabetes but it is unknown whether these lifestyle changes or

medication change the risk for developing diabetes or in children and teenagers. A total of 72 children and teenagers will participate in this study and the study will last for 2 years.

Study Procedure

If you agree to participate in the study there are certain requirements that must be met. The study will be fully explained to you and you will be asked to sign the consent form prior to any study procedures being performed.

You will be seen monthly for the first year and every 3 months during the second year at the Children's Hospital, London Health Sciences Centre (CH, LHSC) at which time blood pressure, height, weight and waist circumference will be measured. Each visit will take about 1 ½ hours. At Screening, 6, 12 and 24 month visits 2 blood samples equal to approximately 2 teaspoons will also be taken and a finger probe test will be done. You will be randomized into a vigorous or moderate intensity 12-week exercise program and expected to attend 3 weekly exercise sessions lasting for 1 hour. This exercise program will take place at the Exercise and Health Psychology Lab, UWO. If you are randomized to the vigorous exercise program the exercise sessions will be more challenging than for the moderate program. You also will participate in weekly 20 minute group sessions (during the same time you come to exercise) where you will learn skills to help you maintain a healthy active lifestyle. There will be weekly group physical activity sessions for an additional 92 weeks after the 12 week randomized phase. At baseline screening, 6 and 12 weeks and 6, 12 and 24 months you will be asked to complete quality of Life and Psychological questionnaires. At baseline screening, 3, 6, 12 and 24 months physical health will be assessed using DEXA scan, electrocardiogram (ECG), ultrasound and blood pressure measurements, as well as fitness and activity (see Entry visit 2 below)

Girls assigned to metformin must have a urinary pregnancy test prior to study entry and this will be repeated every 6 months during the study. If the pregnancy test is positive, they will be required to withdraw from the study. Girls receiving metformin who are sexually active should use an effective birth control method.

Screening Visit (will take approximately 2 ½ hours)

At the Screening Visit at Children's Hospital, London Health Sciences Centre you will be assessed by a social worker and seen by a pediatric endocrinologist.

Entry Visit 1 (will take approximately 1 hour)

This visit will take place at Children's Hospital, London Health Sciences Centre.

During this visit you will have the following procedures performed:

- A fasting blood test when approximately 1-2 teaspoons of blood will be drawn for measurement of insulin, sugar, cholesterol, triglycerides, adipocytokines (fat hormones), liver and kidney function. You will be given a sugar containing drink and two hours later another blood test (less than half a teaspoon of blood) will be taken to repeat the blood sugar measurement.
- Physical examination.

- Vascular assessment (blood pressure, and a finger probe test using thimble-shaped probes on the tips of your fingers to test for early signs of atherosclerosis or hardening of the arteries).
- Dietary assessment using 3-day food record.

Entry Visit 2 (will take approximately 2 hours)

This visit will take place at Exercise and Health Psychology Laboratory, UWO

- DEXA scan (an x-ray used to assess body composition by measuring the amount of fat and muscle in the body).
- Activity will be assessed using an accelerometer to measure activity-related energy expenditure movement. This is a small device, the size of an iPod worn on the right hip during the waking hours for seven days.
- Fitness will be assessed by measuring how well your lungs and heart react to exercise on a standardized treadmill protocol.
- Quality of Life and Psychological questionnaires will be completed. This will take approximately 30 minutes to complete.
- An ECG, which measures the electrical activity in your heart, will be performed. This is a small device about the size of a cell phone which can be worn on your belt. You will be asked to wear it for 24 hours to record your activity in your heart. After the 24 hours you will be asked to return the system to the study clinic.
- Ultrasound will be performed (obtain images of your heart and different blood vessels).
- Vascular assessment (blood pressure, and a finger probe test using thimble-shaped probes on the tips of your fingers to test for early signs of atherosclerosis or hardening of the arteries).

At completion of Visit 2 procedures, if you meet the eligible criteria you will be randomized (like the flip of a coin) to 1 of 4 groups;

1. Lifestyle intervention with placebo (contains no active medication) and standard study (moderate intensity) exercise program.
2. Lifestyle intervention with metformin and standard study (moderate intensity) exercise program.
3. Lifestyle intervention with placebo (contains no active medication) and a vigorous intensity 12 week exercise program followed by the standard study exercise program.
4. Lifestyle intervention with metformin and a vigorous intensity 12 week exercise program followed by the standard study exercise program.

Lifestyle Intervention

Dietary Intervention

You will be assessed by a dietitian, and be advised on nutrition with emphasis on low fat content and increased fiber. You will be seen monthly by the dietitian for the first 12 months, and every 3 months during the second year. Three day food records will be repeated at 6, 12 and 24 months.

Exercise Intervention - Weeks 1 to 12

The first 12 weeks of the exercise program will be conducted by trained staff in the Exercise and Health Psychology Lab at the University of Western Ontario. As mentioned above, you will be asked to exercise three times per week on a cycle ergometer, rower, treadmill, or stepper, or use age-appropriate resistance training equipment for 12 weeks. Exercise sessions will involve a warm-up, exercise portion and a cool down. You will be in the exercise class for the full hour for every session; however fitness level appropriate exercises will be implemented so that you can gradually maintain longer bouts of exercise. Those in the vigorous exercise group will be expected to work at higher intensity (reflected by their heart-rate) than those in the moderate exercise group.

Weeks 13 to Weeks 104

You will be asked to attend weekly group physical activity sessions at the YMCA of Western Ontario, 382 Waterloo Street, London, Ontario. Each session lasting 1 hour and supervised by a fitness specialist. Activities will include the use of steps, dynabands, fit balls and weights. You will be provided with these devices for daily home use. There is no cost to you; the physical activity sessions will be covered by the study.

Family/Behavioural Intervention

You will be asked to see a social worker once a month for the first year, and every 3 months during the second year to review progress, goals and strategies to achieve goals.

One of your parent's will be asked to come to all study visits and to come to a group meeting lasting for 2 hours once every 3 months. At these meetings the study social worker, dietitian, nurse co-ordinator, fitness specialist or a community health worker will meet with families to discuss any problems with making changes in diet and exercise and explore ways to help you make these changes.

Number of Study Visits

During Week 1 to 12 there will be 41 visits:

- Entry – 2 visits
- Exercise visits - 3 visits per week (total of 36)
- Diet and family/behavioral visits – 1 visit per month (total of 3)

During Week 13 to 52 there will be 53 visits:

- Exercise visits - 1 visit per week (total of 40)
- Diet and family/behavioral visits – 1 visit per month (total of 9)
- Parent group visits (total of 4)

During Week 53 to 104 there will be 60 visits:

- Exercise visits – 1 visit per week (total of 52)
- Diet and family/behavioral visits – 1 visit every 3 months (total of 4)
- Parent group visits - total of 4

Metformin Therapy

If you are assigned to receive metformin you will start therapy at 500mg/day, increasing by 500 mg/day every 7 days to a maximum tolerated dose of 2000mg/day taken before the evening meal as a single dose.

Risks

The most common side effects of metformin are: abdominal pain, diarrhea and nausea and these can be prevented or reduced by gradually increasing the dose over 4 weeks.

The most serious risk is lactic acidosis, which is very rare but if very severe can cause coma. This is extremely rare especially in children and teenagers unless there is a kidney or liver problem. A blood sample to check for kidney and liver function will be done at Screening. If abnormal, you will not be eligible to enter the study. Also if you require an x-ray with contrast material at any time, metformin should be temporarily stopped.

Risk of hypoglycemia (low blood sugar) is very rare in association with metformin, if it occurs it will be treated with oral glucose tablets.

Risks of having DEXA scan: This requires exposure to radiation, but the risk is considered very low. The effective radiation dose from this procedure is about 0.01 mSv, which is about the same as an average person receives from background radiation in 1 day.

Risks of having an ECG: the adhesive from these electrodes may cause a small rash which should disappear in a day or two.

Risks of Blood Pressure Measurement: During testing the cuff around your finger may cause your finger to turn slightly blue and feel numb but this goes away quickly when the cuff pressure is reduced. The cuff around your arm will prevent blood from entering your arm for up to 1 minute. There are no risks with stopping blood flow for this duration of time, though the cuff will feel tight around your arm, this sensation goes away immediately upon deflation of the cuff.

Risks of Ultrasound: There are no known risks associated with the use of ultrasound.

Risk of Fitness Assessment: Maximal fitness tests are safe. For clinical tests the estimated risk of a cardiac event is .4 to .5 per 10,000 tests.

Risk of Metformin: It is not known whether or not metformin is safe in pregnant women. In animal studies metformin has not caused any damage to the fetus but animal studies may not predict effects in humans. Therefore, you may not take part in this research study if you are pregnant, breastfeeding or plan to become pregnant while on this study. If you are a woman of childbearing potential, you must discuss birth control measures with your study doctor. To prevent you from becoming pregnant, you will be asked to use medically effective birth control while enrolled in the study such as birth control pills, barrier methods such as a condom or diaphragm, or an intrauterine device (IUD). You must continue using birth control for one month after the end of the study.

If you become pregnant during the study, you will be discontinued from study participation for safety reasons. If you become pregnant within 28 days after you have stopped taking study drug, we ask that you contact your study doctor for safety monitoring. In either case, please make your Obstetrician aware of your study participation. Should you decide to make this information available, your study doctor will ask that you, or your obstetrician, provide updates on the progress of your pregnancy and its outcome.

The finger probe test is radiation free, has no side effects and comfortably rests on the finger tips. It uses a blood pressure cuff which may result in temporary numbness and tingling in the fingers after use.

In addition to the risks listed, there is always the possibility that you may have a side effect that is currently unknown and unanticipated.

Benefits

There is no guarantee that you may benefit directly from this research. Regardless of any individual benefit, the knowledge gained from this study may help other children and teenagers at risk for development of diabetes.

Participation

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care.

Withdraw from the study

The study doctor may stop your participation in the study at any time if decided that it is in your best interest or if you are unable to keep appointments. If you are participating in another study at this time, you are not eligible to participate in this study.

Alternatives to participate

If you decide not to participate in the study you will be offered the standard care, a visit with a dietitian every 6 months.

Reimbursement

There is no charge to you for the participation in the study or costs of tests or procedures directly associated with this study. You will receive up to \$20 for each study visit/or exercise visit to compensate for travel and any other reasonable out of pocket expenses, that are directly related to your participation in the study. If you do not complete the study, you will not receive the payments you would have received after that point.

Compensation for Injury

If you are injured as a direct result of taking part in this study, medical treatment shall be made available primarily through your study doctor and the London Health Sciences Centre. You have not waived any of your legal rights by signing the consent form.

Confidentiality

All study medical records and research materials in which you are identified will be kept confidential and will not be made publicly available, unless required by applicable laws and regulations. If the results of this study are published, no one will know you were a part of the study.

By signing the consent form you allow the review of your study medical records by authorized representatives of Children's Hospital, London Health Sciences Centre, Lawson Health Research Institute, London Health Sciences Centre as well as other doctors, nurses, or personnel involved in the study. Your medical records may be examined in connection with this study or further analyses related to it. If you decide to withdraw from this study, your medical records will be made available as described above.

Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study related records to monitor the conduct of the research.

You have the right to look at your study medical records and request correction of any errors about yourself by contacting the study doctor.

We will be informing your primary physician of your participation in the study as part of routine care.

Your study-related records will be kept for a period of 25 years as per the Health Canada Food and Drug Regulations.

Contact for Further Information

Thank you for taking the time to read the information about this study. If you have any questions or concerns now or at any time about the study, your safety or your rights, please ask your study doctor, his study staff or the contact person(s) indicated below.

If you have questions about your rights as a research participant or the conduct of the study you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute at (519) 667-6649.

If you have any questions during the study, or if you experience any side effects, please contact Dr. Clarson at 519-685-8138 or the study co-ordinator at 519-685-8100.

Consent Form

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Justine Wilson MA Candidate

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.
I will receive a copy of the Letter of Information and signed Consent Form.

Patient's Name/Legally Authorized Representative (Printed)

Patient's Signature/Legally Authorized Representative

Date

Person Obtaining Consent (Printed)

Person Obtaining Consent (Signature)

Date