PARTICIPANT INFORMATION SHEET

Project Title: The independent effects of diet and exercise in the progression and treatment of chronic liver disease.

Investigator: Dr Ingrid Hickman 3240 2804 i.hickman@uq.edu.au

You are invited to participate in a research trial at the Princess Alexandra Hospital investigating diet and exercise in patients with chronic liver disease

Background and Reason for the Study

Weight gain in the Australian population is leading to an increased prevalence of non-alcoholic fatty liver disease (NAFLD), which has the potential to lead to cirrhosis (severe scarring of the liver). Hepatitis C virus (HCV) is also a major cause of chronic liver disease in Australia and is associated with a fatty liver and worsened by obesity. In overweight and obese patients with NAFLD or HCV, a combination of diet changes and increased physical activity can lead to significant improvements in liver disease. However, the individual effects of diet and exercise on liver disease are not known. We propose that in patients with NAFLD and HCV, dietary restriction and different types of physical activity will have independent effects on features of liver disease. In this study we will test your physical fitness and assess dietary intake and compare this to the severity of liver disease.

Length of the Study

Over the next month you will be required to attend 2 appointments at the Princess Alexandra Hospital. These appointments may occur in any order.
Appointment A: 3 ½ hours
Appointment B: 8 hours

Requirements

Appointment A: At your appointment you will be required to have your height, weight. waist and blood pressure measured, undergo fitness testing on a treadmill for 10-20 minutes, have body composition measured using a DEXA imaging machine and a CT scan, provide a blood specimen and complete a dietary and health and well being questionnaire booklet.

You will be asked to walk or run on a treadmill for up to 10 minutes while we measure the amount of oxygen in your breath. Muscle mass and fat mass will be measured by a DEXA machine which is similar to having an x-ray but has about 10% of the radiation of a chest xray. A CT scan will be used to assess the distribution of fat tissue in your body which can help us to determine how much fat is stored under your skin (subcutaneous) and around your vital organs (visceral). CT imaging uses special x-ray equipment to produce multiple images or pictures of the inside of the body and a computer to join them together in cross-sectional views of the area being studied. The images can then be examined on a computer monitor or printed. The effective radiation dose from this procedure is about the same as the average person receives from natural background radiation in three years. It is possible to make these tests on two separate days if more convenient.

Appointment B: Euglycaemic Hyperinsulinaemic clamp assessment of hepatic insulin resistance
Insulin resistance is the term used when your body is not able to use or respond to the insulin it makes. Insulin resistance can occur peripherally (as measured in your blood) or within the liver itself (also called hepatic insulin resistance). The euglycaemic hyperinsulinaemic clamp allows us to detect where in the body insulin resistance might be occurring. The clamp requires you to lie in bed for 4-6 hours while one drip infuses glucose and another drip infuses insulin. The doctor will monitor your glucose levels every 15 mins for 4 hours until a complete balance between insulin and glucose is achieved. We will also take measures of vascular function by placing a pencil-like probe lightly on the surface of the skin at the artery in your wrist, neck and upper thigh. Your blood pressure will also be measured by the usual method involving the inflation of a cuff around your upper arm. We will also measure your resting metabolic rate at the same time, which requires you to simply lie still for 30 minutes on a bed while a machine measures your breathing. Blood tests will include measures of insulin sensitivity, blood lipids and liver enzymes and will exclude other

causes of liver disease such as viral hepatitis and autoimmune disease. Serum from the blood sample and urine may be stored for up to 10 years at this institution. The reason for keeping the samples is that in the future if better tests arise which relate to this research, the blood and urine could be analysed using these new tests. The dietary and health questionnaire will be used to assess your usual dietary intake, smoking and alcohol intake, quality of life and general well being.

Risks/Discomfort
Blood drawing is mildly painful and can cause bruising and, very rarely, fainting, blood clots or an infection at the site. A DEXA scan involves a level of radiation 90% lower than that received during a chest x-ray. The risks associated with the euglycaemic hyperinsulinaemic clamp and test meals are considered low but include discomfort/bruising at the needle site and possible IV line infection. Risk of hypoglycaemia during the clamp is very low due to close medical supervision and 15min testing of glucose levels. A stable isotope of glucose will be used which involves no radiation.

We will ask you to withhold all of your medications on the morning of both tests. A medical doctor will review your medications and advise you to take them at the end of the test as appropriate. If you have diabetes, your diabetic medications will also be withheld. We will monitor your blood sugar levels during the test. If your blood sugar becomes very high (greater than 20 mmol/L), you will be given some short acting insulin to bring the blood sugar level down. This insulin will be given under the skin on the stomach and causes only mild discomfort.

Benefits
You may not receive any personal benefit however your participation in the study will provide you with an intensive medical review. Your participation in the study may help future patients by giving important information about treatment options for chronic liver disease.

Confidentiality
Investigators may need to access your medical chart. Confidentiality of your records is important to us and will be maintained. No personal information will be provided to institutions not involved in this study. In the case of publications arising out of the research, only group data will be published and no individual patients will be identified. You may access the published information on request. All patient files are kept in a locked filing cabinet for up to 10 years. The study has been approved by the Princess Alexandra Hospital Human Research Ethics Committee. If you have questions about your rights as a patient in this study, you may contact The Princess Alexandra Hospital Human Research Ethics Committee and Ethics Manager on 3240 5856 who is an impartial third party not associated with this study. The study adheres to the guidelines of the ethical review process of The University of Queensland, the Queensland University of Technology and the Royal Brisbane and Women's Hospital. If you would like to speak to an officer of these institutions, you may contact the Ethics Officers on 3365 3924 (UQ) or 3864 2340 (QUT) or 3636 5490 (RBWH).

Voluntary Participation
If you decide not to participate in the study, you will continue to receive standard care for your condition. Your participation in this study is voluntary. If you do not participate, this will not affect your future treatment. You are free to discontinue participation in the study at any time without fear of penalty or loss of medical care.

Questions about the research: If you have any questions about the research, you should contact the project staff: Dr Ingrid Hickman 3240 2804 or A/Prof Graeme Macdonald 3240 2701 or Dr Nuala Byrne 3864 3276.

Consent form – PHASE 1

Project Title: The independent effects of diet and exercise in the progression, severity and treatment of chronic liver disease

Investigator: Dr Ingrid Hickman 3240 2804 i.hickman@uq.edu.au

I ……..... consent to take part in the above study.
(print name)

I have read the attached Information Sheet and understand the nature and purpose of this study and any side-effects or risks involved. All my questions have been answered to my satisfaction.

I acknowledge that my involvement in the study may not be of benefit to me.

The opportunity has been given to me to have a friend or relative present when the study was explained.

I understand that taking part in the study is voluntary and I am free to withdraw at any time I wish and this will not affect my clinical management.

I understand that all the information gained in the study will be treated confidentially.

Patient:_____Date:_____

Witness:_____Date:_____

Witness print name:_____

I have explained the nature and purpose of this study to the above participant and have answered their questions.

Investigator:_____Date:_____

PARTICIPANT INFORMATION SHEET

Project Title: The independent effects of diet and exercise in the progression and treatment of chronic liver disease.
Investigator: Dr Ingrid Hickman 3240 2804 i.hickman@uq.edu.au

You are invited to participate in a research trial at the Princess Alexandra Hospital investigating the effect of diet and exercise on chronic liver disease. All participants must have completed Phase 1.

Background and Reason for the Study
Weight gain in the Australian population is leading to an increased prevalence of non-alcoholic fatty liver disease (NAFLD), which has the potential to lead to cirrhosis severe scarring of the liver. Hepatitis C virus (HCV) is also a major cause of chronic liver disease in Australia and is associated with a fatty liver and worsened by obesity. In overweight and obese patients with NAFLD or HCV, a combination of diet changes and increased physical activity can lead to significant improvements in liver disease. However, the individual effects of diet and exercise on liver disease are not known. We propose that in patients with NAFLD and HCV, dietary restriction and different types of physical activity will have independent effects on features of liver disease. In this study we will test the difference between changes in diet, aerobic physical activity and resistance training on the health of your liver. If this hypothesis is correct, we may be able to contribute to improving the advice that doctors can give to patients in order to help maximise patients treatment options.

Length of the Study
Total follow-up required for this study will be 12 months. You will be required to attend an initial intensive intervention for 14 weeks followed by monthly review for up to 12 months. Data collected during the study can be kept on file for up to 10 years.

Requirements
If you are eligible and consent to this study, you will be randomised (a process similar to flipping a coin) to one of 2 groups:

1) **Dietary Intervention**: Individual review by a Dietitian once per week for 14 weeks to achieve a calorie restriction which will enable 0.5kg weight loss per week (approximately 6kg in total)

OR

2) **Circuit Training Exercise Intervention**: Supervised group exercise program with a personal trainer for 45minutes, 3-4 times per week.

Neither you nor your doctor will get to choose which group you are allocated to. This will be randomly assigned after you consent to the project. This is an important aspect of clinical research and you will not be able to change which group you are allocated to.

Within 6-12 months of completion of the exercise/diet intervention, **you will be required to have another liver biopsy** to assess the changes to your liver disease. A liver biopsy is an invasive procedure and is associated with a small but definite risk. While you have already experienced a previous liver biopsy it is important you are aware of the potential risks associated with repeating this procedure. Minor side effects include bruising and pain in around 40% of patients. 1 in 300 to 1 in 1000 patients may experience a major complication which requires hospitalisation e.g. puncture of other organs (lung, gall bladder or bowel) or excessive bleeding. In very rare cases, (1 in 10 000) patients have died following a liver biopsy, but these patients were usually sick to start with (e.g. they already had liver failure or kidney failure or cancer). Blood transfusion and/or surgery may be required for the more serious complications. The risks and discomfort for the biopsy procedure will be explained in detail prior to scheduling the biopsy and your treating physician will be available to determine if it is clinically safe to undergo this procedure at the time of biopsy.

Blood samples will be taken (about 30mls or 2 tablespoons) every 4 weeks during the intensive intervention and every 3 months during follow-up. This is required to assess changes to biochemical and metabolic features of liver disease during the intervention.

In order to measure your usual activity level we will give you a small device called an accelerometer. We will teach you how to wear it. It is about the same size as a pager. You will wear it continuously (except when sleeping and showering) for a week at a time (then you will have a week off) during the lifestyle intervention. In addition, we will also train you to use a heart rate monitor. This is a watch which you will wear whenever you do exercise. It records how long and hard you exercised. We can download the information from the accelerometer and the heart rate monitor to see how active you have been.

During and at completion of Phase 2 (after 12 months of intervention), a number of procedures performed at during Phase 1 will be repeated. These include:

- An euglycaemic hyperinsulinaemic clamp repeated at 12 months: The clamp requires you to lie in bed for 4-6 hours while one drip infuses glucose and another drip infuses insulin. The doctor will monitor your glucose levels every 15 mins for 4 hours until a complete balance between insulin and glucose is achieved. We will also take measures of vascular function by placing a pencil-like probe lightly on the surface of the skin at the artery in your wrist, neck and upper thigh. Your blood pressure will also be measured by the usual method involving the inflation of a cuff around your upper arm. We will also measure your resting metabolic rate at the same time which requires you to lie still for 30 minutes on a bed while a machine measures your breathing.
- The exercise physiologist will repeat a number of fitness tests at 12 months to measure your fitness levels and body composition. This is required to assess the effect of the intervention on your fitness levels and the amount of fat tissue in your body. You will be asked to walk or run on a treadmill for up to 10 minutes while we measure the amount of oxygen in your breath (VO2max test). Muscle mass and fat mass (body composition) will be measured by a DEXA machine which is similar to having an x-ray but has about 10% of the radiation of a chest x-ray. A CT scan will be used to assess the distribution of fat tissue in your body which can help us to determine how much fat is stored under your skin (subcutaneous) and around your vital organs (visceral). CT imaging uses special x-ray equipment to produce multiple images or pictures of the inside of the body and a computer to join them together in cross-sectional views of the area being studied. The images can then be examined on a computer monitor or printed.

Risks/Discomfort

Blood drawing is mildly painful and can cause bruising and, very rarely, fainting, blood clots or an infection at the site. A DEXA scan involves a level of radiation risk similar to an x-ray and will be performed twice through the course of the study. The effective radiation dose from the CT scan is about the same as the average person receives from natural background radiation in three years.

We will ask you to withhold all of your medications on the morning of testing. A medical doctor will review your medications and advise you to take them at the end of the test as appropriate. If you have diabetes, your diabetic medications will also be withheld. We will monitor your blood sugar levels during the test. If your blood sugar becomes very high (greater than 20 mmol/L), you will be given some short acting insulin to bring the blood sugar level down. This insulin will be given under the skin on the stomach and causes only mild discomfort.

There are risks associated with a repeat biopsy and this will be described in detail by your doctor. You need to be aware that the second biopsy is for research purposes only to determine the effect of the intervention and would not normally be required for your clinical management.

Benefits

You may not receive any personal benefit however your participation in the study will provide you with an intensive medical review, dietary assistance and access to exercise expertise. Your participation in the study may help future patients by giving important information about treatment options for chronic liver disease.

Confidentiality

Investigators may need to access your medical chart. Confidentiality of your records is important to us and will be maintained. No personal information will be provided to institutions not involved in this study. In the case of publications arising out of the research, only group data will be published and no individual patients will be identified. You may access the published information on request. All patient files are kept in a locked filing cabinet for up to 10 years. The study has been approved by the Princess Alexandra Hospital Human Research Ethics Committee. If you have questions about your rights as a patient in this study, you may contact The Princess Alexandra Hospital Human Research Ethics Committee and Ethics Manager on 3240 5856 who is an impartial third party not associated with this study. The study adheres to the guidelines of the ethical review process of The University of Queensland, the Queensland University of Technology and the Royal Brisbane and Women's Hospital. If you would like to speak to an officer of these institutions, you may contact the Ethics Officers on 3365 3924 (UQ) or 3864 2340 (QUT) or 3636 5490 (RBWH).

Voluntary Participation
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Questions about the research: If you have any questions about the research, you should contact the project staff: Dr Ingrid Hickman 3240 2804 or A/Prof Graeme Macdonald 3240 2701 or Dr Nuala Byrne 3864 3276.

Consent form - PHASE 2

Project Title: The independent effects of diet and exercise in the progression, severity and treatment of chronic liver disease

Investigator: Dr Ingrid Hickman 3240 2804 i.hickman@uq.edu.au

I ……..... consent to take part in the above study.
(print name)

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I understand that taking part in the study is voluntary and I am free to withdraw at any time I wish and this will not affect my clinical management.

I understand that all the information gained in the study will be treated confidentially.

Patient:_____Date:_____

Witness:_____Date:_____

Witness print name:_____

I have explained the nature and purpose of this study to the above participant and have answered their questions.

Investigator:_____Date:_____