

SUBJECT INFORMATION SHEET AND INFORMED CONSENT FORM

SUBJECT INFORMATION SHEET

Study Title: Anti-Diabetic Drug, Exercise and healthy Diet for knee osteoarthritis with overweight/obesity, a randomized controlled trial (ADDED trial)

Investigator: Dr LAU CHUN MAN

Study Site: Department of Orthopaedics & Traumatology, Queen Mary Hospital, Hong Kong

Subject's Identification: (Subject No.)

You are being invited to take part in a research study. Please take time to read the following information carefully and discuss it with friends, relatives and your family doctor, before you decide whether or not to participate. Please ask us if there is anything that is not clear, or if you would like more information.

This consent form describes in details about the purpose of the research being conducted, the scientific reasons for investigation of this product including the likely benefits/side effects. This document also informs you, as study participant, about your rights and responsibilities for participating in this trial.

What does giving consent for this study mean?

Consent means agreeing to take part in this study. Your participation in this study is entirely voluntary. You have the right to decide if you want to take part in the study or not. It is important that you have the information about this study that you need in order to decide if you want to participate.

You may withdraw consent at any time and request us not to use your samples for subsequent research. This will not affect the way your doctor treats you.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. After taking part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What is the purpose of the study?

Obesity is associated with increased pain with knee osteoarthritis and increase progression of knee osteoarthritis while weight loss intervention has been shown to reduce pain and requirement of total knee replacement. In this study, we will assess using diet modification with exercise, and metformin, a common, safe, diabetes mellitus medication that has been in use for 70 years to achieve better weight control to reduce knee pain. This helps us to understand whether the combined treatment can reduce joint

pain, reduce body weight and improve symptoms and requirement of total knee replacement.

Why have I been chosen?

Your body mass index is regarded as overweight/obesity, and you have knee osteoarthritis.

What do I have to do?

You will be randomly grouped into the intervention group or the control group by a random sequence generated by computer, sealed in an opaque envelope.

If you are randomized to the intervention group, you will have to receive metformin.

If you are randomized to the control group, you will receive placebo.

When first start taking metformin/placebo standard tablets, the dose will increase slowly. This reduces the chances of getting side effects.

For example:

one 500mg dose with or after breakfast for at least 1 week, then

one 500mg dose with or after breakfast and your evening meal for at least 1 week, then

one 500mg dose with or after breakfast, lunch and your evening meal

Both intervention group and control group will receive physiotherapy guided exercise therapy and dietitian guided diet modification to achieve weight control and dietary advice after enrollment into the study and receive further follow up to assess their improvement in knee symptoms, body composition in particular muscle mass and performance, blood test and body weight.

The reduction of fat mass and improvement in muscle mass in treatment group compared with control group will be assessed by Bioelectrical impedance analysis.

What are the benefits of taking part?

Both control and intervention groups will receive more active rehabilitation and weight control intervention through exercise and diet than routine practice and according to existing literature that is beneficial to reduce your knee symptoms and lead to healthier lifestyle.

If randomized to the control group, you will the above diet and exercise therapy.

If randomized to the intervention group, you will additionally receive metformin.

Metformin is a drug that can optimize glycemic control while reducing body weight.

There are evidence showing it also lowers the risk of major cardiovascular events such as stroke, heart attack, or death in adults also with known heart disease. You will be provided with metformin free of charge.

What are the potential risks of taking part?

Metformin is a diabetes mellitus drug that have been in use for 70 years and have been used in non-diabetic persons with very well-studied safety profile.

Metformin is a medicine used to treat type 2 diabetes and gestational diabetes. It's also used to help prevent type 2 diabetes if you're at high risk of developing it. It helps to control blood sugar levels by reducing the amount of glucose produced by the liver and increasing the sensitivity of muscle cells to insulin, which helps the body use glucose more effectively.

Type 2 diabetes is a condition where the body does not make enough insulin, or the insulin that it makes does not work properly. This can cause high blood sugar levels (hyperglycaemia). Metformin lowers your blood sugar levels by improving the way your body handles insulin.

It's usually prescribed for diabetes when diet and exercise alone have not been enough to control your blood sugar levels.

Risks and Side Effects of Metformin:

Gastrointestinal Issues: Nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are the most common side effects.

Lactic Acidosis: Although rare, metformin can cause a serious condition called lactic acidosis, which is a buildup of lactic acid in the blood. Symptoms include muscle pain, difficulty breathing, stomach pain, dizziness, and feeling cold.

Vitamin B12 Deficiency: Long-term use of metformin can interfere with the absorption of vitamin B12, potentially leading to deficiency

Hypoglycemia: While metformin alone usually does not cause low blood sugar, the risk can increase when it is combined with other diabetes medications or insulin:

Kidney Function: Metformin should not be used by individuals with severe kidney disease, as it is excreted by the kidneys and poor kidney function can increase the risk of lactic acidosis.

Who may not be able to take metformin?

- Metformin is not suitable for some people. To make sure it's safe for you, tell your doctor before starting the medicine if you:
- have ever had an allergic reaction to metformin or other medicine
- have uncontrolled diabetes
- have liver or kidney problems
- have a severe infection
- are being treated for heart failure or have recently had a heart attack
- have severe problems with your circulation or breathing difficulties
- drink a lot of alcohol

You may need to stop taking metformin before having surgery and certain medical tests. Tell your doctor if you need to have:

- a test such as an X-ray or scan involving the injection of a dye that contains iodine into your blood
- surgery where you'll be put to sleep (given a general anaesthetic)

Low blood sugar:

- Metformin does not usually cause low blood sugar (known as hypoglycaemia, or "hypos") when taken on its own. But hypos can happen when you take metformin with other diabetes medicines, such as insulin or gliclazide.

Early warning signs of low blood sugar include:

- feeling hungry
- trembling or shaking
- sweating
- confusion
- difficulty concentrating
- It's also possible for your blood sugar to go too low while you're asleep. If this happens, it can make you feel sweaty, tired and confused when you wake up.

Low blood sugar may happen if you:

- take too much of some types of diabetes medicines
- do not eat meals at regular times or skip meals
- are fasting
- do not eat a healthy diet and are not getting enough nutrients
- change what you eat
- exercise too much without eating enough carbohydrates
- drink alcohol, especially after skipping a meal
- take some other medicines or herbal remedies at the same time
- have a hormone disorder, such as an underactive thyroid (hypothyroidism)
- have kidney or liver problems
- To prevent hypoglycaemia, it's important to have regular meals, including breakfast. Try not to miss or delay a meal.
- If you're planning to exercise more than usual, make sure you eat carbohydrates like bread, pasta or cereals before, during or after exercise.
- Always carry a fast-acting carbohydrate with you, like sugar cubes, fruit juice or some sweets, in case your blood sugar level gets low. Artificial sweeteners will not help.
- You may also need to eat a starchy carbohydrate, like a sandwich or a biscuit, to maintain your blood sugar for longer.

Are there any long-term side effects?

- Metformin is safe to take for a long time. It will not make you put on weight, and may even help you lose some weight.
- It also helps keep your cholesterol at a healthy level.

References:

American Diabetes Association (ADA): The ADA provides guidelines and information on the use of metformin for the management of type 2 diabetes.

National Institute for Health and Care Excellence (NICE): NICE guidelines offer recommendations for the treatment of type 2 diabetes, including the use of metformin.

FDA: The U.S. Food and Drug Administration provides detailed information on the approved uses, side effects, and risks associated with metformin.

Peer-Reviewed Medical Journals: Articles and studies published in journals: the Journal of the American Medical Association (JAMA) and The Lancet

Will this study preserve my radiological images and clinical information and use it for future research?

This study will preserve the radiological images and clinical information for comparison and reference in further studies of similar nature. However, only the radiological images and clinical information will be used, and all personal information will not be used or retained, so as to achieve deidentification of data and protection of the confidentiality of personal data. Histology tissue will not be used in future studies.

Will I need to pay / will there be any extra expenses?

There will be no charge for you to participation in the study.

Will my taking part in this study be kept confidential?

Your personal data relevant to this study will be collected during the study process. All collected personal data and medical information relevant to this study about you will be strictly confidential. You will only be identified by a study number and initials in the study database, and no personal identity will be disclosed when study results are being reported and/or published.

Your records may be audited by the hospital's Institutional Review Board (IRB) and/or may be inspected by regulatory authorities, to check that the study is being carried out correctly. Your identity will remain confidential unless, for example, disclosure is required by law.

Under the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance, Cap 486, you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study.

By signing and dating this Consent Form, you agree to and do give up, waive, disclaim, adjust and in any way abrogate all of the above-mentioned rights. For any query, you should consult the Privacy Commissioner for Personal Data or his office (Tel No. 2827 2827) as to the proper monitoring or supervision of your personal data protection so

that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

What will happen to the results of the research study?

When the results of this study become available, they may be published in a medical journal. You can ask your study doctor for this information. You have the rights of access to personal data and known study results, in accordance to local practice.

Who has reviewed the study?

The ethics committee namely the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) has reviewed and approved this study.

Contact for further information

For questions about your rights as a study subject, call the Secretary, the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) at: 2255 4086.

For questions about the study or reporting of adverse events, call the study coordinator Ms. Sue at telephone number: 2255 4413.

Reference:

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INFORMED CONSENT FORM

Study Title: Anti-Diabetic Drug, Exercise and healthy Diet for knee osteoarthritis with overweight/obesity, a randomized controlled trial (ADDED trial)

Subject's Identification: (Subject No.)

1. Investigator's confirmation

I confirm that I fully informed the subject _____ of the nature, risks, and consequences of the above named study as well as the management of the subject's medical data. The subject has been given a copy of the Subject Information Sheet.

_____	_____	_____
Date of Signature	Investigator's Printed Name	Signature

2. Subject's confirmation

I confirm that I have been fully informed by Dr. _____ of the nature, risks, and consequences of this study and the management of the clinical data. I have been given a copy of the Subject Information Sheet and I am in agreement with the content. All my questions have been answered to my satisfaction. I hereby give, of my own free will, my consent to participate in the study under the terms and conditions contained in the said Subject Information Sheet and fully agree to the management of the clinical data.

_____	_____	_____
Date of Signature	Subject's Name	Signature

3. Confirmation of Witness, (where applicable)

I attest that the information in this Informed Consent Form and any other written information (including the said Subject Information Sheet) were accurately explained to, and apparently understood by the subject and that informed consent was freely given by the subject.

_____	_____	_____
Date of Signature	Witness's Name	Signature