Participant Information & Consent Form

Protocol Title: **The ECoM Study:** Effect of Carnitine Supplementation on Progression of Carotid Plaque in the Metabolic Syndrome

You are being invited to participate in a voluntary research study. Should you choose not to participate in this study your care will not be adversely affected in any way.

The purpose of this study is to evaluate the effect of L-carnitine therapy (medication) on the progression of atherosclerosis, narrowing of blood vessels, in patients diagnosed with metabolic syndrome (described below). While taking this therapy you will be providing blood samples and carotid artery (neck) scans by 3-D ultrasound. Ultrasound is a safe and non-painful procedure (about 15-30 min), that allows us to study changes in fatty deposits in your arteries.

In order to decide whether you wish to participate in this research study you should understand the risks and benefits involved in order to be able to make an informed decision. This process is known as informed consent. This consent form provides detailed information about the research study. The doctor or a member of the study staff will discuss the study with you and answer any questions. Once you understand the study, you will be asked to sign this form if you wish to participate in this study. You will be given a signed copy of the consent to keep in your records.

Dr Amer Johri, Cardiologist, will be supervising this study at the Kingston General Hospital/Queen's University, Department of Medicine, P: 613-533-6000 x75432, Email: cinq.research@gmail.com. This study has been reviewed and approved by Dr. Albert Clark, Chair of the Queen's University Health Sciences and Affiliated Teaching Hospitals' Research Ethics Board. This study is supported by funds from SEAMO (Southeastern Ontario Academic Medical Association) Innovation Fund and The Heart and Stoke Foundation of Canada.

Purpose of the Research

Metabolic syndrome is a name for a group of heart disease risk factors that occur together: obesity, diabetes, high blood pressure, and high cholesterol. Patients with metabolic syndrome have a high risk of developing narrowing and blockages of blood vessels. These occur when fat and cholesterol build up in the walls of blood vessels and form "plaque also", known as atherosclerosis. High amounts of plaque deposits can lead to strokes and heart attacks. We do not fully understand what causes metabolic syndrome and current treatments do not treat the syndrome as a whole, but rather treat individual components (cholesterol, sugars, blood pressure). We would like to have new ways of slowing down or reversing the progression of this disease to reduce the risk of heart conditions. Monitoring the amount of plaque deposits, with ultrasound, is a useful way to monitor disease progression and determine if therapy is helpful.

L-carnitine is a nutrient supplement normally found in some plants and meats as well as being produced by our bodies to increase our energy levels. Animal studies suggest L-carnitine reduces the deposition of plaque in blood vessels, while human studies have shown improvements in blood

pressure, cholesterol, and sugars in diabetic patients. It may be indirectly associated with fat and sugar metabolism. L-carnitine is currently available as a natural supplement without a prescription and is approved by Health Canada for other uses (carnitine deficiency). In Canada, L-carnitine is not approved for MetS. Therefore it is an investigational drug in this study. An investigational drug is one that has not been approved for general use by the Health Canada but is under investigation in clinical trials regarding its safety and efficacy.

Our goal is to study whether supplementation of L-carnitine does in fact prevent or reverse the buildup of plaque in the blood vessels of patients with metabolic syndrome. This study is being conducted at 2 centres in Ontario. Overall, we anticipate enrolling approximately 160 participants, 80 patients per centre.

Study Procedures

Patients who enter the study will be divided into two groups. The groups will be decided through a random selection process (like flipping a coin). Each group will receive either L-carnitine (the investigational medicine) or placebo (inactive ingredient).

GROUP 1: L-carnitine administered by mouth; 4 oral pills twice a day for six months.

or

GROUP 2: Placebo (ingredient Microcrystalline Cellulose (Avicel)) administered by mouth; 4 oral pills twice a day for six months.

The dose of L-carnitine provided will be 2000 mg daily (2x 500 mg capsules twice a day (BID) = 4 total per day) for six months; the duration of treatment. Placebo will be Microcrystalline Cellulose (Avicel) powder pills (2x capsules twice a day = 4 total per day) for six months.

This is a blinded study, which means that, neither you nor the medical staff will know what treatment group you have been assigned to. This blinding procedure is necessary to prevent bias and to assess the true effects of L-carnitine treatment on carotid plaque accumulation. The placebo looks exactly like the L-carnitine used for the treatment of atherosclerosis but is made up of a material that does not have any effect. The physician and research coordinators will monitor you closely while you are receiving either treatment.

To be able to retrieve additional related health information, we are asking you for your family physician name and contact information. In order to schedule visits, you will be asked to give your email address, mailing address, contact telephone numbers, and an alternate contact with contact information.

Study Schedule and Time Commitment (Total of 5 visits - about 8 hours in total, please note this is an estimate and these times may vary during the study and exclude communications outside scheduled visits):

First visit (Screening/Baseline), 2-3 hours:

After providing informed consent, we will measure your blood pressure, height, weight, waist to hip measurement along with other background information and cardiovascular family history. The study also involves the collection of blood samples. You will need to fast for 10-12hrs before your blood work. Approximately 1 tablespoon (15 mL) of blood will be taken to measure the levels of sugar, fat,

and L-carnitine in your blood. A baseline 3Dultrasound scan of your neck area will be done to measure the amount of plaque in your arteries. This scan will take approximately (15-30 min).

Second visit (Randomization), 0.5-1 hour:
If you meet the requirements for inclusion in the study (blood test results and amount of plaque), you will be randomized to a treatment group. Your blood pressure, weight, waist to hip measurement will be done and a review of the medications you are currently taking will be done. You will be given your study medication and you will be asked to keep a log of when you take your medication. We will also request that you track your intake of red meat as it naturally contains L-carnitine.

Follow-up visits, 0.5-1 hour each (2 visits):
You will have two follow up visits at 1 and 3 months. At this time the research coordinator will measure your blood pressure, weight, waist to hip measurement, review the medications you are currently taking, your red meat consumption, your study medication count and log, and any side effects.

Final Visit, 2 hours:
You will have your final visit at 6 months after you have completed taking your study medication). As with the previous visits, we will measure your blood pressure, weight, waist to hip measurement, review the medication you are currently taking, your red meat consumption, your study medication count and log, and any side effects. A repeat blood sample approximately 1 tablespoon (or 15 mL) of blood will be taken to measure the levels of sugar, fat and L-carnitine in your blood, and a final 3D ultrasound of the neck will be performed

Possible Risks
L-carnitine is an amino acid naturally produced by the body and is abundant in meat. The US Food and Drug Administration (FDA) have approved L-carnitine for treating L-carnitine deficiency for example in strict vegetarians, dieters, and premature infants. No significant toxicity with L-carnitine, (500-2000 mg/day in divided doses) in humans has been reported. *Please do not use thyroid hormone, AZT, doxorubicin, isotretinoin, valproic acid during the study period as it may interact with L-carnitine.*

There is insufficient information on the effect of L-carnitine in pregnancy, therefore we recommend to women of child bearing age (pre-menopause) to use accepted contraceptive methods throughout the study, such as birth control pill, transdermal patch, progesterone implant, IUD, vaginal ring, condom used with intra vaginal spermicide, etc. The duration of contraception should be at least 30 days prior to and also 30 days post of last dose of the study drug.

Minor side effects of L-carnitine may include a fishy body odour, nausea, diarrhea, and seizures (in people prone to seizures). Please report immediately to your study coordinator/doctor/nurse should any unusual symptoms occur at 613-533-6000, x75432.

Risks associated with obtaining a blood sample include: minor pain, bruising, and on rare occasions, infection. There are no risks associated with 3D ultrasound of the neck. Ultrasound is a safe non-invasive type of x-ray.

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

Possible Benefits

The information researchers obtain from this study may help others in the future and this is the main anticipated benefit of this study. It is not known if receiving the active medication will result in any benefit, therefore we cannot promise that you will be helped by being in this study. If there are benefits they may include: improvement in blood pressure, cholesterol levels, glucose and insulin levels, decreased fatty deposits in your arteries, and decreased risk of death. Should you receive placebo your care will not be compromised and you will receive the same standard of care as any other cardiovascular patient at the clinic.

Alternatives

The current standard of care for metabolic syndrome is the treatment of the risk factors associated with the syndrome (obesity, high cholesterol or triglycerides, high blood pressure, high blood glucose). There is currently no single treatment of the syndrome as a whole. This may include therapy with blood pressure medications, cholesterol reducing drugs and insulin, which you will be kept on throughout the study. The alternative to participating in the study is not to participate. You will continue to receive the best medical therapy, without prejudice whether or not you choose to take part in this study.

Participation

Participation in research is voluntary. A letter will be sent to your family or specialized physician(s) informing them of your participation in our study. You will continue taking all of your current medications for any medical conditions you may have, such as diabetes, hypertension, high cholesterol, etc. Please inform your research coordinator of any changes in your medications during the study. You are free at any time to stop your involvement in the study. This will not affect your medical care in any way. If you decide to withdraw from this study, we request that you contact the research coordinator at 613-533-6000, x75432. If possible we would request you participate in the final follow up visit and procedure (information, blood sample, and neck scan).

You will be informed, in a timely manner, of any new information on L-carnitine or options for new treatments, which may affect your willingness to continue taking part in this study. If you have any concerns about the study, you may want to discuss these with your family physician.

Stopping the Study

The study investigators may stop the study, or your participation in it, at any time without your consent. If this happens, it might be as a result of new information that is learned from the study. If the study is stopped or you are removed from the study you will be informed and notified of the reason.

Compensation

Parking compensation will be provided at each visit. You will not be paid to participate in this study. There is no fee for participating in this study. Study costs will be paid for by the study budget. Provincial health insurance will pay for any care or tests beyond what is required in this study. If you are not eligible for provincial health insurance, your health plan or other insurance will need to pay for care or tests beyond what is covered by this study. If you are injured as a result of taking part in this study, medical care will be provided until resolution of the problem. By signing this consent form, you do not waive your legal rights nor release the investigator(s) from their legal and professional responsibilities.

Rights and Confidentiality

Personal health information will be collected during the study. Any information learned during the study will be kept confidential. Your health information will be viewed by study researchers and officials or committees that oversee the study to make sure it is conducted in accordance with Health Canada or Queen's University Research Ethics Board. The results and ultrasound images of this study may be published in the medical literature, but your name and personal information will not be revealed.

By signing this document you do not give up any legal rights you may have in the case of negligence of a legal fault of anyone who is involved with the study.

With your consent, we will also use your OHIP number to link the information we collect from your health records and your study results with that of the information available at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, such as cardiac related events or outcomes. ICES is an independent, non-profit organization whose infrastructure funding and access to Ontario's large administrative databases is provided by the Ontario Ministry of Health and Long Term Care. ICES links de-identified population-based health information at the patient level in a way that ensures privacy and confidentiality of patients. ICES is named as a section 45(1) Prescribed Entity in Ontario's Personal Health Information Protection Act (PHIPA). Review, audit and approval of ICES' policies, practices and procedures related to data privacy and security are performed tri-annually by the Information and Privacy Commissioner of Ontario (IPC). This approval/review document is available at www.ipc.on.ca. After all the required data transfer and linkages have been made, any information that might identify you specifically (such as your date of birth and OHIP number) will be permanently removed from the data set. After this, only your anonymous study ID number will be used. Data at ICES will be stored securely in encrypted electronic storage (computer coded).

Signature Page

To participate in this study (ECoM), you must sign this page. By signing this page, you are confirming the following:

❑ I have read and understand the consent form for this study.

❑ I have had the purposes, procedures, and technical language of this study explained to me.

❑ I have been given sufficient time to consider the above information and to seek advice if I chose to do so.

❑ I have had the opportunity to ask questions which have been answered to my satisfaction.

❑ I am voluntarily signing this form. I will receive a copy of this consent form for my information.

❑ I consent to providing blood samples for the purpose of general health monitoring and of fat, sugar, insulin, and L-carnitine.

❑ I consent to undergo a carotid ultrasound (ultrasound of the neck vessels).

❑ I consent to participate and be randomized for this study if I meet the required criteria (test results).

❑Yes or ❑No I authorize the transfer of my OHIP number, date of birth, and study results to ICES as explained in this consent form for linkage to health data available at ICES.

If at any time I have further questions, problems or concerns, I can contact the research coordinator and principal investigator Dr. Amer Johri at 613-533-6000, x75432. The head of the Department of Medicine, Dr. Stephen Archer, can be contacted at 613-533-6327. If I have any question about my family member's rights as a research subject, I may call Dr. Albert Clark, Chair of the Queen's University Health Sciences and Affiliated Teaching Hospitals' Research Ethics Board at 613-533-6081.

Patient Name (Print)	Signature	Date & time
Individual Conducting Informed Consent Discussion (Print)	Signature	Date & time

I, or one of my colleagues, have carefully explained to the subject, the nature of the above research study. I certify that to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits and risks involved in participating in this study.

Dr. Amer Johri (If investigator did not sign above)	Signature	Date & time

Follow-Up Contact Information:

Patient Information	
Name:	
Telephone (Home): Telephone (Cell):	
Email:	
Address:	
Alternate Information	
Name:	
Telephone (Home): Telephone (Cell):	
Email:	
Address:	
Family Physician	
Name	
Telephone	
Email:	
Address	