Beneficial effects of the amino-acid food supplement L-Citrulline in Participants with Peripheral artery disease

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Some studies have reported improved vascular function with the supplementation of L-arginine in participants with CVD. Several clinical studies have also begun the investigation of L-arginine supplementation in participants with PAD. This is...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON43867

Source
ToetsingOnline

Brief title
CIPER

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
peripheral artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: ERC Top Grant

Intervention

Keyword: L-citrulline, Nitric oxide signalling, Peripheral artery disease

Outcome measures

Primary outcome

The primary efficacy parameter is the change in absolute claudication distance

(measured as treadmill-measured maximum walking distance) in the randomized

groups.

Secondary outcome

The secondary efficacy parameters include arterial and endothelial functions

and measurements of the metabolites of L-citrulline metabolism.

Study description

Background summary

Peripheral artery disease (PAD) is a common manifestation of atherosclerosis, narrowing of a blood vessel due to plaque formation. People with PAD have a higher risk of cardiovascular disease (CVD). Nitric oxide (NO), a chemical released by endothelial cells (lining cells of the blood vessels), has been shown to play an important role in PAD and CVD. This is because NO dilates blood vessels, regulates blood flow and blood pressure and maintains the integrity of the blood vessel by preventing platelets sticking to the vessel wall. NO production is regulated by a class of enzymes known as the NO synthases. These enzymes synthesize NO from its amino acid substrate, L-arginine in the presence of co-factors.

Loss of the protective actions of NO, a cardinal feature of endothelial dysfunction, contributes to the development of CVD. Decreased NO production has been observed under conditions of oxidative stress, a process during which damaging free radical production is increased. This reduced NO production through oxidative stress may be harmful as most CVD and related risk factors coincide with oxidative stress. Finding ways to increase or maintain NO production is hence important.

Study objective

Some studies have reported improved vascular function with the supplementation of L-arginine in participants with CVD. Several clinical studies have also begun the investigation of L-arginine supplementation in participants with PAD. This is particularly important as currently there are limited options available to medically manage intermittent leg pain resulted from PAD. Although some of these short-term clinical trials suggested that oral L-arginine improved walking distance or improved walking speed in participants with PAD, these results were not consistent. Further, only 1% of the oral supplemented L-arginine is available for the NO production as the rest is metabolised by the body. A better way to provide the body with substrate to produce NO is therefore needed. The natural amino acid and food component, L-citrulline has been suggested to be a good candidate for this purpose.

L-citrulline, named after watermelon citrullus vulgaris from which it was first isolated, is a natural precursor of L-arginine. Studies have shown that L-citrulline is metabolised by the body to a lesser degree compared to L-arginine and hence is an effective precursor of arginine in peripheral tissues, including endothelial cells. Oral L-citrulline supplementation also eliminates some of the unwanted effects associated with oral arginine supplementation and it is well tolerated without known side effects. In addition, L-citrulline is a supplement that is available over-the-counter. Thus, oral supplementation of L-citrulline may be a new intervention strategy in participants with PAD.

We hypothesize that the oral food supplement L-citrulline, unlike L-arginine, reverses endothelial dysfunction.

Study design

The primary aim of this trial is to examine whether the oral food supplement L-citrulline has any effect on clinical status, walking distance, arterial and endothelial function in participants with PAD.

We will use a double-blinded crossover design in which patients serve as their own controls. Patients who are enrolled will have two 'treatment' periods of twelve weeks with a wash-out period of 4 weeks in between. Patients will be randomly assigned to get L-citrulline in the first and placebo in the second period and vice versa.

Intervention

After a screening phase of 3 weeks, there will be a 'zero-point' measurement en then the first 'treatment' period of 12 weeks starts (placebo or food-supplement). Then there is a wash-out phase of 4 weeks after which the second 'treatment' period starts (food-supplement or placebo) In both periods, after 2 weeks and at the end of the period, a measurement of primary and

secondary outcomes will be done: a questionnaire has to be filled out, treadmill test and flow-mediated dilation or endo-PAT(for vessel function). The follow-up will take another 4 weeks and will end with a phone call to check for the condition of the patient and possible side effects.
Since every patient gets both placebo and the food-supplement, every patient is his/her own control.

For the patients in the Catharina Hospital in Eindhoven, the treadmill tests will be performed by the patients treating physiotherapist (part of the Claudicationet).

Study burden and risks

During the study, patients will take L-citrulline and placebo during 12 weeks. No side effects or negative effects are expected from taking these substances.

Patients will have to do a few extra visits to the hospital that do not belong to the standard visits. During the visits, blood will be drawn and the vascular function will be measured in the fore-arm by using a blood pressure cuff, which can give an unpleasant feeling.
Treadmill tests will also be performed which can cause the pain/complaints that the patients also experiences as part of his condition.

Contacts

Public
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* 40 years or older males and postmenopausal women;
* male participants must agree to using an adequate form of contraception during the study period;
* 6-month history of stable intermittent claudication (IC) due to PAD;
* PAD secondary to atherosclerosis with significant claudication (Fontaine class II defined as IC, or Fontaine class III defined as pain at rest);
* IC characterised by pain, ache, cramp, numbness or severe fatigue involving muscles of one or both lower extremities, reproducibly provoked by walking and relieved by rest;
* ankle-brachial index (ABI) at rest of <0.9 and at least 25% decrease in ABI within 1 min during exercise recovery;
* capacity to walk more than 2 min/15 meters but no more than 12 min on a treadmill using the Skinner-Gardner protocol;
* walking limited by claudication, not coexisting conditions; and
* difference between two consecutive baseline exercise treadmill tests of <25% during the 3-weeks run-in period; and
* no change in medications or physical activity within 3 months prior to enrolment.

Exclusion criteria

* Women of child-bearing potential;
* Current enrolment in another clinical trial and/or ingestion of another investigational product within the past 30 days before enrolment;
* PAD of non-atherosclerotic nature;
* Fontaine class IV i.e. ulcer or gangrene;
* leg amputation above the ankle;
* peripheral vascular surgery, sympathectomy, peripheral angioplasty or stent insertion within the previous 3 months;
* myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery within the previous 3 months;
* uncontrolled hypertension (resting SBP >190 or DBP >115 mmHg);
* hypotension (SBP <90mmHg);

* type I diabetes, proliferative retinopathy;
* history of disease state or surgery that affects gastrointestinal absorption;
* significant renal disease (serum creatinine >3.0 mg/dl);
* liver disease (transaminase > 3x upper limit of normal, bilirubin >1.5 times upper limits of normal);
* history of treatment for any malignancy within the past 5 years, or evidence of active malignancy other than squamous cells or basal cell carcinoma of the skin;
* serious infection or hypotension associated with sepsis in the last month;
* cerebrovascular infarct in the last 3 months;
* autoimmune disorders (e.g. systemic lupus erythematosis, ulcerative colitis);
* any other acute or chronic medical condition that in the opinion of the investigators increases the likelihood that the participant would be unable to complete the study;
* unwillingness to discontinue arginine- or L-citrulline-containing products, pentoxifylline, L-carnitine, or prostacyclin for at least 1 month prior to and during the study; and
* conditions other than PAD that limit walking distance.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2016
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO

Date:	07-12-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT02521220
CCMO	NL54573.100.15