Glycocalyx restoration in treatment resistant hypertension: a proof of concept, randomized, double-blind, placebo-controlled study

Published: 26-09-2024
Last updated: 30-01-2025

Primary Objective: • To assess whether the food supplement Endocalyx lowers blood pressure in patients with treatment resistant hypertension.Secondary Objectives: • To study the effect of Endocalyx on office blood pressure and 24-hour blood pressure...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON57024

Source
ToetsingOnline

Brief title
Endocalyx for treatment resistant hypertension

Condition

- Other condition

Synonym
high blood pressure, hypertension

Health condition

hypertensie

Research involving

Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Hartstichting + Nierstichting + Microvascular Health Solutions,Microvascular Health Solutions

Intervention

Keyword: blood pressure, glycocalyx, hypertension

Outcome measures

Primary outcome

24-hour systolic blood pressure

Secondary outcome

Secondary outcomes will be used to investigate the mechanism by which Endocalyx may improve hypertension and to assess the safety in patients with treatment resistant hypertension:

- 24-hour blood pressure parameters: daytime blood pressure, night-time blood pressure, dipping status

- Office blood pressure.

- Percentage of patients that needed additional antihypertensive drugs during the study

- Percentage of patients that required lowering of antihypertensive drugs during the study

- Percentage of patients with an office blood pressure <140/90 mmHg

- Total body water and body weight.

- Hemodynamic parameters: heart rate, cardiac output and total peripheral resistance.

- Microcirculation analysis

- 36-item short form health survey (SF-36)

- EQ-5D-5L questionnaire

- Incidence of (serious) adverse events.

- Skin sodium content as measured with 23Na-MRI

- The modulating effect of sodium intake, sex and kidney function on the

abovementioned parameters

Study description

Background summary

Hypertension is the most important risk factor for cardiovascular disease and all-cause mortality worldwide. Although antihypertensive therapy is readily available, half of the patients with hypertension have an uncontrolled blood pressure (BP). If BP is uncontrolled despite using >=3 antihypertensive drugs, it is considered to be treatment resistant hypertension (TRH). Among treated adults with hypertension the prevalence of TRH is 10-15%, which equals 675,000 patients in the Netherlands. Subjects with TRH have a 50% higher risk for cardiovascular or renal disease, or death than subjects with normal hypertension. Currently, no treatment is available for subjects with uncontrolled BP despite maximum drug therapy and invasive interventions such as renal nerve ablation or carotid baroreceptor activation therapy are considered in a research setting.

Besides antihypertensive drugs, lifestyle changes are crucial to control BP. Reduction of dietary sodium intake is by far the most effective lifestyle intervention and can lower systolic/diastolic BP with 23/9 mmHg in subjects with TRH. However, because of large amounts of sodium in processed foods, patients often fail to adhere to a lifelong low sodium diet, which is an important cause of TRH. For example, the average sodium intake in TRH patients is 187 mmol/day while a daily intake <87 mmol is advised. We therefore need a new treatment, which ideally targets the sodium overload and sodium sensitivity of BP in TRH patients.

Tissue sodium accumulation
Long-term sodium balance studies demonstrated that sodium can be osmotically inactivated by negatively-charged glycosaminoglycans that are present in the

skin and the glycocalyx, an intravascular layer of glycosaminoglycans. As a result, sodium retention is not accompanied by water retention or a BP increase. In addition, the glycocalyx prevents sodium to be transported to the skin where high sodium content impairs microcirculatory function.

Hypertensive patients have a damaged glycocalyx and are thus not able to neutralize the negative effects of sodium excess or prevent sodium leakage to the skin, which contributes to sodium sensitivity of BP. We previously demonstrated that glycocalyx restoration with oral glycosaminoglycans reduced BP in subjects with proteinuria. We expect that glycosaminoglycan supplementation will restore the glycocalyx, prevent skin sodium accumulation and lower BP in TRH subjects.

Endocalyx is food supplement that consists of polysaccharides, amino sugars and antioxidants, which has been designed to restore the glycocalyx. The polysaccharides are a natural component of the glycocalyx and are adsorbed by the glycocalyx. Amino sugars, such as glucosamine, are precursors for the biosynthesis of polysaccharides and antioxidants protect the endothelial polysaccharides from breakdown. Endocalyx has demonstrated to improve microvascular health by 50% and decrease the perfused boundary region, which indicates improved glycocalyx health.

Potential impact on cardiovascular burden of disease
In the Netherlands, approximately 675,000 patients have TRH. The average annual incidence of cardiovascular events and mortality in these patients is around 4.65% and 3.45%, respectively. When extrapolating these proportions to the Dutch TRH population, this would account for approximately 31,388 cardiovascular events and 23,288 deaths annually.

Previous studies have demonstrated that the expected 8 mmHg decrease in systolic BP by Endocalyx will result in a 27% decrease in stroke, 17% decrease in coronary events and heart failure, and 13% decrease in cardiovascular mortality Consequently, about 4,118 cardiovascular events and 878 deaths could be prevented annually in the population of subjects with TRH.

Study objective

Primary Objective:
• To assess whether the food supplement Endocalyx lowers blood pressure in patients with treatment resistant hypertension.

Secondary Objectives:
• To study the effect of Endocalyx on office blood pressure and 24-hour blood pressure profiles (daytime BP, night-time BP, dipping status) in subjects with treatment resistant hypertension.
• To evaluate the percentage of patients achieving an office blood pressure

<140/90 mmHg.
• To assess whether sodium intake, sex or kidney function modulates the effect of Endocalyx on blood pressure.
• To define the effect of Endocalyx on microcirculatory health in subjects with treatment resistant hypertension.
• To assess the effect of Endocalyx on total peripheral resistance in treatment resistant hypertension subjects.
• To assess whether Endocalyx improves quality of life.
• To estimate the potential impact of Endocalyx on long-term cardiovascular protection and health care costs.
*

Study design

We will use a proof-of-principle randomized, placebo-controlled, double-blind trial to investigate the effects of Endocalyx in patients with treatment resistant hypertension. Patients will be randomly assigned (1:1) to the food supplement Endocalyx or placebo, 4 capsules per day, in addition to their current medication for 12 weeks. Patients will be recruited from the Internal Medicine outpatient clinics of Amsterdam UMC, Onze Lieve Vrouwe Gasthuis (OLVG) and Flevoziekenhuis.

Patients will make a total of 5 study visits and we will conduct 3 scheduled telephone calls. All study visits will be conducted at Amsterdam UMC, location AMC.

Intervention

Patients will be randomly assigned to the food supplement Endocalyx or placebo in addition to their current medication for 12 weeks. Patients in the Endocalyx and placebo arm will receive 4 capsules per day. This treatment will be double blinded.

Study burden and risks

The overall risk of the Endocalyx food supplement is low. The individual ingredients of the supplement are already used as dietary supplements. Large randomized controlled trials with the individual ingredients, some with higher dosages of the ingredients than in the Endocalyx supplement, revealed no major adverse effects and showed the safety of the individual ingredients. In the pilot study with the supplement, no serious adverse effects were reported. One side effect that was reported was dizziness because of the effect on reducing blood pressure. The blood pressure is measured at every study visit and the dosages of the anti-hypertensive medicine can be altered if needed. Moreover, the occurrence of adverse effects is documented and evaluated at the end of every month. Patients are provided with the telephone number of the

investigator that they can call in the case of a serious adverse event.

Contacts

Public
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Treatment resistant hypertension defined as
a. an uncontrolled office BP (>=140/90 mmHg).
b. is on a regimen of >=3 adequately dosed antihypertensive agents of different classes, including a diuretic, at maximum tolerated dose based on investigator judgment.
2. Stable diuretic and antihypertensive treatment for the previous 3 weeks.
3. Subject, or legal representative, has voluntarily signed and dated an Informed Consent Form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has

been explained and the subject has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed.

Exclusion criteria

1. Age <18 years.
2. Estimated glomerular filtration rate (eGFR) <20 ml/min/1.73m2 measured by the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine formula and the 2012 cystatin C CKD-EPI formula.
3. A mean seated systolic blood pressure of at least 180 mm Hg or a diastolic blood pressure of at least 110 mm Hg (if the patient did not take their regularly scheduled blood pressure medication prior to the visit, a blood pressure re-test is allowed within 2 days.
4. Known secondary hypertension
o Obstructive sleep apnea syndrome
o Pheochromocytoma
o Primary hyperaldosteronism
o Renal artery stenosis
o Cushing syndrome
o Uncontrolled or untreated hyperthyroidism
o Aortic coarctation
5. An acute coronary syndrome, stroke, transient ischemic attack or cardiovascular surgery in the last 3 months.
6. Hospitalization for heart failure in the past 3 weeks.
7. Dialysis treatment or expected initiation of dialysis within 3 months of screening.
8. Women of child bearing potential who are not taking adequate contraception (i.e. <1% failure rate). Acceptable methods of contraception for female patients enrolled in the study include the following:
o Surgical sterilization (tubal ligation);
o Intrauterine device for at least 12 weeks before screening;
o Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before screening; or
o Diaphragm used in combination with spermicide
9. Planned surgery in the next 12 weeks.
10. Major surgery in the previous 4 weeks.
11. Use of prednisolone >5 mg/day
12. Use of any other investigational drug.
13. Presence of significant comorbidities (e.g., advanced malignancy, advanced liver disease) with a life expectancy of less than 1 year.
14. A psychiatric, addictive or any disorder that compromises ability to give truly informed consent for participation in this study.
15. Known hypersensitivity to seaweed, corn, artichoke, grape, melon or to any of the excipients of Endocalyx.

15. Bekende overgevoeligheid voor zeewier, maïs, artisjok, druif, meloen of voor één van de hulpstoffen van Endocalyx.
16. Known hypersensitivity or allergies for milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat and soybeans.
17. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption.
18. (Only applicable to participants interested in the additional measurements using the 7T sodium MRI) Known contra-indication for MRI scans. Metallic foreign body, certain drug pumps, hydrocephalus pump, external prosthesis (e.g. artificial limb), intrauterine device, vascular clips/stents/pumps, cardiac implantable devices, neuro-stimulator, artificial valves, implanted lenses, prosthesis or cochlear implants, bones screws, plates, claustrophobia and orthopnea might be considered a contra-indication for MRI. In all of these cases, the MR operator will search MRISafety.com to see if the person can be scanned safely. If it is not clear whether the subject can be safely scanned with the 7T MRI, a colleague from Spinoza will be contacted to discuss whether this patient can be scanned safely.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-01-2025
Enrollment:	64
Type:	Actual

Ethics review

Approved WMO Date:	26-09-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
CCMO	NL85685.018.24