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Do the metabolites produced by gut bacteria influence the skin via the bloodstream?

Submission date
17/10/2023

Recruitment status
No longer recruiting

Registration date
23/10/2023

Overall study status
Completed

Last Edited
06/03/2025

Condition category
Urological and Genital Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Metabolites derived from foods or gut bacteria, such as putrefactive compounds as represented by Indoxyl sulfate (IS) and trimethylamine N-oxide (TMAO), are considered to be circulating through blood vessels to reach the skin and influence skin properties or microbiome. IS in the blood is completely derived from gut bacteria. Likewise, 70% and 30% of TMAO are derived from gut bacteria and food, respectively. In a previous study, the concentration of these putrefactive compounds in the plasma samples from CKD patients with haemodialysis was markedly higher than that in the plasma samples from healthy subjects. Based on the hypothesis, it is assumed that the relationship of these putrefactive compounds between blood and SC samples is more easily evaluated through the comparison between healthy subjects and CKD patients undergoing haemodialysis. It would support the adequacy of the gut-skin axis evaluation model based on the compounds. While many reports on the relationship between gut bacteria and skin properties exist, there are still no findings that these putrefactive compounds produced by gut bacteria are detected from the skin by using a minimally invasive method to relate the gut and the skin. In the previous study, the study team developed a novel, convenient and minimally invasive method using polyvinyl alcohol (PVA), which is a main component of cosmetic peel-off masks, to detect various skin components from the very same sample. The aim of this study is to confirm whether there is a relationship between the amounts of several putrefactive compounds among stool, plasma and stratum corneum (SC) samples collected by PVA. It is also expected that several compounds detected will be common in human stool, plasma and SC samples collected from the same subjects. There is a possibility that compounds other than the putrefactive compounds will be found which could connect the gut with the skin.

Who can participate?
Healthy volunteers and CKD patients undergoing haemodialysis aged over 18 years old

What does the study involve?
Firstly, during screening (V1), the subjects will be asked to complete an eating habits questionnaire. Subjects should collect one stool sample at one occasion in 2 separate tubes 0-5 days prior to sampling day (V2; 7 days later than the screening day V1) and store them cooled in the portable fridge until return to the site on V2. The subjects will also receive a daily defecation questionnaire based on the Bristol Stool Form Scale during V1 and will be asked to return the

completed questionnaire at V2. At V2, samples will be collected from healthy subjects and CKD patients with haemodialysis. For CKD patients undergoing haemodialysis, V2 should be planned right before the next haemodialysis session. Samples that will be required include stool, blood and SC samples collected by PVA (forehead, left cheek, nose and left forearm). Subjects will be advised not to wash or apply cosmetics to the sampling area for at least 12 hours prior to V2. A skin assessment will be done prior to SC sampling. Subjects will be asked to complete the 5-D itch scale. The microbiome and compounds in the samples will be analysed.

What are the possible benefits and risks of participating?
Benefits:
1. The findings will be obtained about the influence of the metabolites of gut bacteria on other organs and the interaction between gut and skin or other organs via blood by developing comprehensive analyses of stool, plasma and SC samples.
2. The discovery of novel compounds will be expected except for the putrefactive compounds which are derived from gut bacteria or foods and which could also directly influence the skin.
3. It could lead to the development of a novel diagnostic tool as an alternative method of the blood test using minimally invasive methods for detecting the conditions in the body.

Risks
There are no risks of taking part in this study.

Where is the study run from?
Yakult Honsha European Research Center for Microbiology VOF (Belgium)

When is the study starting and how long is it expected to run for?
April 2023 to March 2025

Who is funding the study?
Yakult Honsha (Japan)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
YHER23-GSA

Study information

Scientific Title
Assessment of the direct involvement of putrefactive compounds/uremic toxins produced by gut bacteria in the skin environment through a blood stream

Study objectives
It is hypothesised that metabolites derived from foods or gut bacteria, such as putrefactive compounds/uremic toxins, are circulating through blood vessels to reach the skin and influence skin properties or microbiome. The concentrations of the putrefactive compounds produced by gut bacteria such as indoxyl sulfate (IS) and trimethyl N-oxide (TMAO) in the stratum corneum (SC) samples are expected to be proportional to the concentrations in the plasma. As it is reported that the concentration of these compounds in the plasma of chronic kidney disease (CKD) patients undergoing haemodialysis is markedly higher than in healthy subjects, these concentrations in SC samples are also expected to be higher in CKD patients than in healthy subjects.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 22/09/2023, Liège University Hospital-Faculty Ethics Committee (C.H.U de LIEGE, Site du Sart Tilman, Avenue de l'Hôpital, 1, Liège, 4000, Belgium; +32 4 323 21 58; ethique@chuliege.be), ref: 2023-246

Study design
Cross-sectional study single-centre study

Primary study design
Interventional

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Chronic kidney disease patients with haemodialysis

Interventions

This is an interventional study without treatment given to subjects. Stool, plasma and stratum corneum (SC) samples will be collected from 20 healthy subjects and 20 CKD patients undergoing haemodialysis. Recruiting on screening day V1 (day -7) will be continued until the number of subjects at the timepoint of sample day V2 (day 0; 7 days +/- 2 days after V1) reaches 20 in each group and all samples can be collected.

The concentration of putrefactive compounds/uremic toxins, indole, indoxyl sulfate (IS), p-cresol (pCS), trimethylamine N-oxide (TMAO) and ammonia (NH3), other metabolites and bacteria will be measured in stool, plasma and SC samples.

Sample collection
One stool sample at one occasion will be collected in 2 separate tubes 0-5 days before V2 and will be stored at -80°C. Each tube will contain a minimum of 2.0 g of stool. Two 10.0 ml blood samples will be collected in 2 K2 EDTA tubes after antecubital venipuncture during V2. Two samples of 5.0 ml plasma will be obtained after 10 minutes of centrifugation and stored at -80°C. During V2, after 30 minutes of acclimation at 24°C (+/- 3°C) and 40% humidity (+/- 10%), SC samples will be collected from 4 x 6 cm2 each (or 3 x 6 cm2 in case there is not enough space for 4 x 6 cm2) on the forehead, left cheek and left forearm. Likewise, SC samples will be collected from 3 x 6 cm2 each (or 2 x 6 cm2 in case there is not enough space for 3 x 6 cm2) on the nose. Polyvinyl alcohol (PVA) gel which is a main component of cosmetic facial masks will be put on the forehead, left cheek and left forearm using a pipette in a rectangle mould (or in the areas marked by a pen at the 4 edges) of 4 x 6 cm2 or 3 x 6 cm2 and put likewise on the nose of 3 x 6 cm2or 2 x 6 cm2. The PVA gel will be spread with a spatula. After drying for 30 minutes, the PVA-gel can be peeled off with tweezers and put in a 2ml tube and will be stored at -80°C. Subjects will be advised not to wash or apply cosmetics to the sampling area for at least 12 hours before sampling.

Intervention Type
Other

Primary outcome(s)
The concentration of trimethylamine N-oxide (TMAO) and indoxyl sulfate (IS) in SC samples in healthy subjects and CKD patients using ELISA kit and CE-TOF MS and so on at day 0 (V2)

Key secondary outcome(s))
The concentration of TMAO and IS in plasma samples in healthy subjects and CKD patients using ELISA kit and CE-TOF MS and so on at day 0 (V2)

Completion date
31/03/2025

Eligibility

Key inclusion criteria
1. Informed consent obtained before any study-related activities
2. Female or male aged 18 years or older
3. Only for CKD patients: CKD patients with haemodialysis
4. Is willing and able to collect stool at home 0-5 days before V2, store the samples in appropriate conditions and return the samples within the required timeframe
5. Understand the French language (reading, writing, speaking)

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
40

Key exclusion criteria
1. Language barrier, mental or legal incapacity, unwillingness or inability to understand or not being able to participate in the study
2. Has any severe skin disorders such as but not limited to psoriasis, atopic dermatitis, eczema
3. Applied cosmetics to the body sites, which are used as the sampling and analysis area, within 12 hours prior to sampling day (V2)
4. Only for CKD patients: CKD patients without haemodialysis
5. Has an active infection as judged by the investigator
6. Has immunosuppressive therapy
7. Has a body mass index > 35 kg/m2
8. Has inflammatory bowel disease
9. Has an active malignancy
10. Has experienced a cardiovascular event in the past three months prior to V1
11. Has had a transplantation
12. Has used non-steroidal anti-inflammatory drugs within the past one month prior to screening (V1)
13. Has used AST-120 within the past three months prior to V1
14. Use of disallowed concomitant medications and concomitant products
15. Females of child-bearing potential who are pregnant, breastfeeding or are not using adequate contraceptive methods (e.g., oral contraceptive, intrauterine device, abstinence)
16. Any clinically significant disease which in the Investigator’s opinion could interfere with the safety of the study subject or with the results of the study
17. Participation in another interventional clinical study or receipt of any investigational product within 1 month prior to V1
18. Patients who received agents containing cathartic ingredients, such as antibiotics and laxative drugs, within 4 weeks prior to V1
19. Subject has smoking habits (more than 5 cigarettes per day) or alcohol abuse (more than 21 units of alcohol per week)
20. Subject used a chemical peel containing retinoic acid, hydroxy acid, salicylic acid and glycolic acid within one month prior to V2
21. Subjects are vegan
22. Anything that can make SC sample collection difficult (such as having a beard to collect the SC sample from the left cheek)

Date of first enrolment
30/10/2023

Date of final enrolment
13/03/2024

Locations

Countries of recruitment
Belgium

Study participating centre
ATC Pharma sa
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Sponsor information

Organisation
Yakult Honsha (Japan)

ROR
https://ror.org/03wmnrc91

Funder(s)

Funder type
Industry

Funder Name
Yakult Honsha

Alternative Name(s)
Yakult

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Japan

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be included in the subsequent results publication.

IPD sharing plan summary
Published as a supplement to the results publication