Effects of oral iron supplementation on the gut microbiome and plasma uremic toxin levels in patients with chronic kidney disease

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This study assesses the effect of oral iron supplementation on gut-derived plasma uremic toxin levels in patients with chronic kidney disease (CKD) and with iron deficiency. The main research questions to be answered are:1. Does oral iron...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Iron and trace metal metabolism disorders
Study type	Observational invasive

Summary

ID

NL-OMON41855

Source
ToetsingOnline

Brief title
Effect of oral iron on gut-derived uremic toxin levels in CKD

Condition

- Iron and trace metal metabolism disorders
- Renal disorders (excl nephropathies)

Synonym
Iron deficiency in CKD

Research involving
Human

Sponsors and support

Primary sponsor: Laboratoriumgeneeskunde
Source(s) of monetary or material Support: Ministerie van OC&W,subsidieaanvragen lopende bij Nutricia Research Foundation en JANIVO stichting

Intervention

Keyword: Chronic Kidney Disease, Gut microbiome, Iron supplementation, Uremic toxins

Outcome measures

Primary outcome

Blood uremic toxin levels (13 uremic toxins: hippurate, indoles (indoxyl sulfate, indoxyl glucuronide and indole-3-acetic acid, tryptophan metabolites (kynurenine, kynureninic acid and quinolinic acid), phenols (phenyl acetic acid, phenyl sulphate, phenyl glucuronide, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF), p-cresyl sulfate and p-cresyl glucuronide), before, during, and after iron treatment.

Secondary outcome

• Faecal uremic toxin levels (13 uremic toxins; see above), before, during, and after iron treatment

• Gut microbiome composition, before, during, and after iron treatment

• Gut microbial proteolytic activity by faecal ammonia, before, during, and after iron treatment

• Blood ammonia levels, before, during, and after iron treatment

• Faecal iron content (for correlation with the gut microbiome composition)

• Other blood parameters: Hb (hemoglobin), MCV (Mean Corpuscular Volume), Fe, TIBC (Total iron binding capacity), ferritin, CRP (C-reactive protein), creatinine (estimation GFR).

o The transferrin saturation will be calculated based on TIBC and Fe.

Study description

Background summary

There is a high prevalence of anemia in patients with chronic kidney disease (CKD), as a result of chronic inflammation. To correct anemia, patients are often treated with iron, given orally or parenterally. Our previous experiments in a kinetic model of the human large intestine have shown that the provision of iron to a human gut microbiota changed its composition and increased protein fermentation, which resulted in a more toxic microbial metabolome. Furthermore, we recently investigated the influence of protein intake on plasma uremic toxin levels in healthy volunteers who were randomized to either a high protein diet or a low protein diet for 2 weeks. In the high protein diet, we observed a significant increase in plasma levels of indoxyl sulfate as well as significant increases in the urinary excretion of indoxyl sulfate, indoxyl glucuronide, kynurenic acid, quinolinic acid and p-cresyl sulfate. Comparable results were obtained in a rodent study. Together, this raises the question whether the administration of iron to patients with CKD contributes to gut microbial protein fermentation and increased production of uremic toxins. Although it is not yet fully clear whether uremic toxins are involved in the pathways leading to progression of CKD, p-cresol and indole derivates (the most studied uremic toxins) have been associated with mortality, cardiovascular disease and progression of CKD.
We hypothesize that oral iron supplementation in iron deficient predialysis CKD patients changes gut microbiome composition, and causes an increase in faecal and plasma uremic toxin levels, due to stimulation of the proteolytic activity of the gut microbiota.

Study objective

This study assesses the effect of oral iron supplementation on gut-derived plasma uremic toxin levels in patients with chronic kidney disease (CKD) and with iron deficiency. The main research questions to be answered are:

1. Does oral iron supplementation cause an increase of uremic toxin levels in the faeces and plasma of predialysis CKD patients?
2. Does oral iron supplementation stimulate gut microbial protein fermentation in predialysis CKD patients?
3. What is the effect of oral iron supplementation on the composition of the gut microbiome of predialysis CKD patients?
4. Does the gut microbiome recover from the iron intervention and does it

change back to the situation before intervention?

Study design

Longitudinal study

Study burden and risks

With regarding to treatment with ferrous fumarate there are no extra risks associated with participation in this study, as this a therapy is a standard regimen for iron deficient predialysis CKD patients. To be complete we here mention the adverse effects related to this therapy: mild constipation (1-10%), diarrhoea (0.1-1%) and allergic skin responses (rash, urticaria, itch, erythema, photosensibilisation) (0.01-0.1%). Other events that have been recorded are nausea, aching stomach, vomiting, anorexia, black colouring of the stools (Farmacotherapeutisch kompas; accessed online on 6-11-2014).

Participation in this study involves the withdrawal of 8 extra blood samples (3-6 mL) over the course of 4 months. It also involves in-home collection (and short-term storage) of faeces at 9 time points, and the completion of a simple food questionnaire at the same time points. Patients from the region of the city of Nijmegen will be included, it is therefore possible to visit the patient at home to collect blood samples and the faecal samples. This reduces the number of site visits by the patient. The risks and burden for the patients can therefore be considered as minimal. To answer our research questions predialysis CKD patients is the most related group, as this group is most vulnerable for an increase in circulating uremic toxins that will not be efficiently cleared by the kidneys.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age range: 18-80 years
2. CKD stage III-IV (GFR of 15-60 ml/min /1.73m2)
3. Iron deficient and an indication for treatment with ferrous fumarate, that is Hb < 7 mmol/L, TSAT (transferrin saturation) <20% and ferritin < 200 µg/l, in the presence of a CRP < 10 mg/L).
4. Living in the region of Nijmegen, that is within 20 km from Radboudumc

Exclusion criteria

1. Patients already under treatment with iron (orally or intravenously), or finished iron treatment <= 4 weeks before start of the trial.
2. Patients using over the counter iron supplements / iron fortified products
3. Constipation (defecation less than 3 times a week).
4. Treatment with antibiotics <= 4 weeks before start the trial. If antibiotic treatment is required during the trial, patients are excluded from the trial.
5. Start of Sevelamer treatment during the trial (patients already on Sevelamer treatment and which is continued do not have to be excluded).
6. Hb < 4.5

Study design

Design

Study type: Observational invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-11-2015
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	19-02-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-03-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL51531.091.14

Study results

Date completed:	17-06-2016
Actual enrolment:	6