Insights in proximal and distal tubular iron reabsorption by studies on urinary iron excretion in human health and disease

Published: 16-06-2016
Last updated: 17-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON43424

Source
ToetsingOnline

Brief title
Renal iron reabsorption in human health and disease

Condition

- Other condition
- Nephropathies

Synonym
Renal disease, systemic iron overload

Health condition

ijzerstapelingsziekten

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Iron, Kidney, Reabsorption, Urine

Outcome measures

Primary outcome

The main study parameters are the level of urinary iron parameters (total iron, transferrin, NTBI and LPI relative to urinary creatinine concentration) in all study groups.

Secondary outcome

The secundary study parameters are the level of blood iron parameters (total iron, transferrin, NTBI, LPI and ferritin), (e)GFR, CRP, urinary albumin concentration relative to urinary creatinine concentration, a panel of specific proximal and distal tubular dysfunction/injury markers (KIM-1, L-FABP, GST-a for proximal and H-FABP, GST-pi, for distal tubules, respectively) relative to urinary creatinine concentration and urinary pH.

Study description

Background summary

The body is able to regulate iron uptake and storage, but has limited ability to regulate iron excretion. Systemic iron bound to the iron transport protein transferrin (ferri-transferrin) is at least partly filtered by the glomerulus of the kidney into the renal tubular lumen and, subsequently, reabsorbed by the

proximal and distal renal tubules in the form of ferri-transferrin and/or non-transferrin bound iron (NTBI). As a result of this, hardly any iron is found in urine in healthy individuals. As a consequence, disturbed dietary iron uptake, e.g. from the intestine in hereditary hemochromatosis or from multiple blood transfusions in *-thalassemia or Diamond Blackfan anemia, can result in systemic iron overload, which is known to affect multiple organs of the body (e.g. liver, heart). In addition, systemic iron overload can result in increased iron exposure to the kidney, which is associated with renal failure. However, the physiological mechanisms of iron handling by the kidney are not fully elucidated and have not been examined in pathological conditions of systemic iron overload or kidney injury. In addition, renal iron reabsorption by the renal tubules is hardly examined in vivo. A better understanding of renal iron reabsorption will provide novel leads for treatment strategies to i) improve the prognosis of kidney injury and ii) increase iron excretion in patients with systemic iron overload.

Study objective

We aim to gain insights in proximal and distal tubular reabsorption of iron, transferrin, NTBI and labile plasma iron (LPI). To this purpose, we will study urinary iron, transferrin, NTBI and LPI concentrations relative to urinary creatinine concentration in healthy volunteers and patients with i) compromised renal tubular function (tubulopathy); and ii) patients with increased iron filtration (patients with systemic iron overload).
We hypothesize increased urinary iron excretion in: i) patients with tubulopathy, since we predict that renal uptake of filtered ferri-transferrin will be reduced in case of compromised tubular function; and ii) patients with systemic iron overload, since the increased levels of ferri-transferrin and NTBI in the tubular lumen are likely to exceed the reabsorption capacity of the renal tubules.

Study design

Cross sectional study.

Study burden and risks

Participation in this study involves the collection of blood (one 3 ml tube) and urine (one spot urine sample) at one time point. As these study procedures are routine in diagnostic practices for these diseases and can be combined with diagnostic practices, the risks and burden for the patients can be considered negligible. Patients using iron chelation medication (e.g. deferasirox) will be asked to withhold the use of this medication for at least 4 days, in order to prevent biased urinary iron measurements by excretion of the iron-chelator-complex.
Because we expect that urine iron levels are determined by glomerular

filtration of systemic circulating iron and by tubular reabsorption, we will include subjects with abnormal body iron levels and tubular function, i.e. subjects with systemic iron overload and subjects with tubular dysfunction, respectively, next to healthy controls.

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

Healthy volunteers: age 18-80 years of age.
Subjects with tubulopathy: age 18 - 80 years, diagnosed with tubulopathy by treating physician (e.g. Fanconi syndrome, Dent's disease, Wilson's disease, cystinosis, tubulo-interstitial nephritis (TIN) or suffers from tubulopathy secondary to e.g. multiple myeloma of secondary nephrogenic diabetes insipidus (sNDI)). This group also comprises subjects with tubulopathy and glomerulopathy: 18-80 years of age, proteinuria (EKR> 0.2 g/ 10 mmol

creatinine), tubular dysfunction (urinary excretion of *1-microglobulin (>50 ug/min) and/or *2-microglobulin (>1 ug/min).
Subjects with systemic iron overload: age 18-80 years of age, diagnosed with HFE-hereditary hemochromatosis, b-thalassemia major or intermedia, or Diamond Blackfan anemia by treating physician, with transferrin saturation (TSAT) > 70%.

Exclusion criteria

Urinary tract infection, menstruating (female), use of iron chelation medication.
Healthy volunteers will be excluded in case of a known history of renal diseases or systemic iron overload.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-07-2016
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Date:	16-06-2016
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-10-2016
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	NL56138.091.16