Pilot study to investigate whether oral phosphorus binders can reduce FGF23 levels and can influence vascular function as measured by pulse wave velocity in patiens with chronic kidney disease stage 3 (eGFR 30-60 ml/min/1,73 m2).

Published: 29-04-2010
Last updated: 15-05-2024

Aim of this study proposal· To establish whether oral phosphorus binding is able to reduce FGF23 levels in patients with CKD stage 3.· To evaluate if a reduction of serum phosphate and FGF23 improves vascular function as measured by pulse-wave-...

Ethical review	Approved WMO
Status	Pending
Health condition type	Nephropathies
Study type	Observational invasive

Summary

ID

NL-OMON36731

Source
ToetsingOnline

Brief title
Effect van fosfaat verlaging op FGF23 en bloedvaten

Condition

- Nephropathies

Synonym
chronic kidney disease, CKD, renal failure

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Genzyme

Intervention

Keyword: FGF23, phosphate, pulse wave velocity

Outcome measures

Primary outcome

Serum FGF23 and phosphaturia before and after 8 weeks of treatment with

sevelamer-carbonate and change in PWV

Secondary outcome

Pulse Wave Velocity measured before and after the treatment with Sevelamer.

Study description

Background summary

Over the last decade it has become clear that patients with end-stage renal disease and patients with chronic kidney disease have a severely enhanced risk for cardiovascular morbidity and mortality. This elevated risk cannot be explained completely by traditional factors like hypertension and hyperlipidemia, well-known to be present in this patient population.

In the search for factors that might contribute to this enhanced cardiovascular risk, the role of renal disease-induced abnormalities in calcium-phosphorus metabolism have become apparent. Recently it was shown that levels of serum phosphorus, calcium and parathormone (PTH) all have U-shape relationships with survival in dialysis patients. In addition there is demonstration that vascular calcification, especially of the coronary artery system, is positively associated with cardiovascular mortality. Likewise in patients with CKD, phosphorus level is associated with cardiovascular outcome. Furthermore, in large observational studies the use of active vitamin D, both in dialysis patients and in predialysis patients, correlates with

improved mortality rates.

Recently, Fibroblast Growth Factor 23 (FGF-23) was identified as a novel and important hormone in phosphate metabolism. FGF-23 decreases phosphate reabsorption in the kidney, due to by down regulation of the expression of Sodium-Phosphate co-transporters in the proximal tubule. In addition, FGF-23 also inhibits 1α-hydroxylase expression, resulting in decreased synthesis of 1,25-dihydroxy vitamin D which could lead to decreased intestinal calcium reabsorption and hypocalcemia, as well as impaired vitamin D-mediated suppression of PTH, and possibly attenuate beneficial pleiotropic effects of activation of the vitamin D recepter. On top of this, it was recently shown that FGF-23 upregulates 24-hydroxylase, which catabolizes all vitamin D metabolites, further inducing a vitamin D deficient state. Vitamin D deficiency (both 25- and 1,25 hydroxylized cholecalciferol) is associated with cardiovascular malfunction.

Recently, FGF-23 was identified as an independent risk factor for mortality in a large hemodialysis cohort. Preliminary data demonstrated exactly the same in predialysis patients with or without diabetes. We aim to further explore the role of FGF-23 in the cardiovascular morbidity of these patients. Since there is epidemiological evidence that FGF-23 level is independently associated with clinical outcome, and because there is biological plausibility that FGF-23 actually modulates the natural history of cardiovascular disease of uremia, we hypothesize that targeting FGF-23 is a legitimate goal for treatment. In the current pilot proposal we expect to demonstrate that it is possible to lower FGF-23 pharmacologically, using phosphate binders, as has been shown convincingly in mice. This could pave the way to proceed with an interventional trial, targeting FGF-23, aiming to improve cardiovascular endpoints.
As mentioned FGF-23 is independently associated with cardiovascular outcome. This association remains after correction of phosphate and also remains if patients use 1,25-dihydroxy vitamin D. (Gutierrez et al. NEJM 2008). The mechanism in which FGF-23 influences cardiovascular status is not yet known. Our hypotheses is that FGF-23 might have a direct influence on the vesselwall since it is known that there is a FGF-23 receptor on the vessel wall. For this reason, and for the reason that vascular function can be influenced over a short time period (eg Kelly et al. Hypertension 2001), whe want to evaluate vascular function bij measuring Pulse Wave Velocity

Study objective

Aim of this study proposal
· To establish whether oral phosphorus binding is able to reduce FGF23 levels in patients with CKD stage 3.
· To evaluate if a reduction of serum phosphate and FGF23 improves vascular function as measured by pulse-wave-velocity (PWV)

Study design

Design
Pilot study in which 20 patients with CKD stage 3 (eGFR 30-60 ml/min/1,73 m2) with high normal serum phosphorus levels will be treated with sevelamer-carbonate (Renvela®) 2,4 g before breakfast and diner for 8 weeks. Patients remain on their usual diet.

Study burden and risks

Laboratory investigations:
* Two weeks and immediately before, after 8 week sevelamer-carbonate treatment as well as two weeks after stopping sevelamer-carbonate:
- in plasma: creatinine, urea, potassium, calcium, phosphate, c-term FGF23, 25OH vitamin D, 1,25 (OH)2-vitamin D, PTH
- in 24h urine collection: phosphaturia, calciuria, creatinine clearance, total protein, urea.
* during the sevalamer-carbonate treatment after one week:
-serum phosphate

Pulse-wave-velocity:
-Two measurement in the the period of two weeks before starting the treatment with Sevelamer. One measurement immediately after stopping the treatment with sevelamer and again one after the two weeks wash out.
(this takes four times half an hour, maximum one hour. The measurement is an painless procedure)

The use of once to twice daily the study medicine (powder for oral suspencion) Renvela. Renvela is a phosphate binder. Phosphatebinders can cause intestinal complaints such as nausea, vomiting, pain in the upper abdomen and constipation. Further sometimes dyspepsia or diarrea. Very rare (< 0,01%) are some cases of intestinal obstruction or ileus.

An X-ray of the abdomen to evaluate the possible existence of vascular calcification. This burdens the patiënt with X-radiation. For one X-ray, the radiation burden is 0,2 mSV. In comparison with the yearly burden of natural sources, which is between 2 to 5 mSv, this is relatively low. For a low dose of radiation, the incidence of mortality through cancer caused by radiaton is estimated 0,04 to 0,07 per sievert (0,00004 to 0,00007 per milliSievert).

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.patients with eGFR 30-60 ml/min/1,73 m2
2.serum phosphorus level <1,49 mmol/L and >0,9 mmol/L
3.age >18 year
4.informed consent

Exclusion criteria

1. known allergy or intolerance for sevelamer-containing drugs
2. patients with heart failure
3. Use of phosphate binder therapy
4. Patients dependent on tube-feeding or those with malabsorption syndrome
5. rapidly deteriorating renal function
6. pregnant woman
7 patient with kidney transplantation

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2010
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	renvela
Generic name:	sevelamer
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-04-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2011
Application type:	Amendment
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

ID: 25966
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2009-016787-36-NL
CCMO	NL31055.029.09
OMON	NL-OMON25966