Effect van fosfaat verlaging op FGF23 en bloedvaten.
Effect of phosphate reduction on FGF23 and bloodvessel function.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25966

Source
NTR

Health condition

English:
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 twice daily for 8 weeks. To investigate wheter phospate reduction can reduce FGF23. FGF23 is independently associated with mortality in patients with kidney disfunction. And to investigate wheter reduction of phosphate and FGF23 leads to a change is bloodvessel function as being measured by PWV (Pulse Wave Velocity)

Dutch:
Pilot onderzoek waarin patiënten met chronische nierschade stadium 3 (eGFR 30-60 ml/min/1,73 m2), met nog een normaal serum fosfaat, worden behandeld met sevelamer-carbonate (Renvela®) 2,4 g, twee maal daags gedurende 8 weken. Onderzocht zal worden of fosfaat reductie FGF23 kan verlagen. FGF23 is een factor die onafhankelijk geassocieerd is met mortaliteit bij patiënten met een nierfunctiestoornis. Verder wordt gekeken of verlaging van fosfaat en FGF23 mogelijk een direct effect heeft op de vaatwand, gemeten met de PWV (Pulse Wave Velocity).

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum (VUmc) Amsterdam
Source(s) of monetary or material Support: -VUmc, nephrology department
-Genzyme Corporation, Cambridge, USA

Intervention

Outcome measures

Primary outcome

Serum FGF23 and phosphaturia before and after 8 weeks of treatment with sevelamer-carbonate.

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.

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, Fibroblast Growth Factor 23 (FGF-23) was identified as a novel and important hormone in phosphate metabolism. FGF-23 was identified as an independent risk factor for mortality.

We aim to further explore the role of FGF-23 in the cardiovascular morbidity of these patients. We hypothesize that targeting FGF-23 is a legitimate goal for treatment to reduce cardiovascular morbidity. In the current pilot we expect to demonstrate that it is possible to lower FGF-23 pharmacologically, using phosphate binders.

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 we want to evaluate vascular function bij measuring Pulse Wave Velocity.

Study objective

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 design

Total duration of the studie is 12 weeks.

Time points in weeks:

1. Time point -2: Measurement of PWV, baseline laboratory investigations of bloodsamples en urinesamples and x-ray lateral abdomen;

2. Time point 0: Measurement of PWV and laboratory investigations of blood- and urinesamples (patients acts as their own control in this way). Start of tratment 8 weeks with sevelamer -carbonate;

3. Time point 1: Measurement of serum phosphate;

4. Time point 8: Stop tratment wiht Sevelamer-carbonate.
Measurement PWV and laboratory investigation of bloodsamples and urinesamples (after treatment);

5. Time point 10: Measurement PWV and laboratory investigation of bloodsamples and urinesamples (after wash-out).

Intervention

Patients will be treated with sevelamer-carbonate (Renvela®) 2,4 g before breakfast and diner for 8 weeks. Patients remain on their usual diet.

Contacts

Public
De Boelelaan 1117
Annet Bouma-de Krijger
Amsterdam 1081 HV

The Netherlands
+31 (0)20 4442673
Scientific
De Boelelaan 1117
Annet Bouma-de Krijger
Amsterdam 1081 HV
The Netherlands
+31 (0)20 4442673

Eligibility criteria

Inclusion criteria

1. Patients with eGFR 30-60 ml/min/1,73 m2;

2. Serum phosphorus level <1,49 mmol/L and >1,0 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.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non controlled trial

Control: N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-06-2010
Enrollment:	20
Type:	Anticipated

Ethics review

Positive opinion

Date:	23-06-2010
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 36731
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL2257
NTR-old	NTR2383

Register	ID
CCMO	NL31055.029.09
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON36731

Study results

Summary results
N/A