The CPH-MBD cohort

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Chronic Kidney Disease – Mineral and Bone Disorder

The CPH-MBD cohort

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1. General information

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2. Overall aim

Persons with chronic kidney disease (CKD) have a 3-fold increased risk of bone fracture and a 10-fold increased risk of cardiovascular disease than the general population. These increased risks are related to the disturbances in the mineral metabolism, and this clinical entity is termed Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD)[1].

The overall aim of the present project is to explore factors that may predict or associate with the development of bone and cardiovascular disease in patients with CKD and hopefully provide insight into underlying mechanisms and pathophysiological pathways for future treatment and prevention.

In a sub study, we aim to explore the calcium and phosphate balance in patients with CKD and describe how these associates with each other as well as the kidney function (eGFR).

3. Background

Chronic kidney disease (CKD) is a chronic condition where the excretory kidney function (estimated glomerular filtration rate (eGFR)) is reduced and/or markers of kidney damage is present (often presented as albuminuria). CKD is classified into stages CKD G1-5 according the severity of the reduction in eGFR[2].

The prevalence of CKD is increasing world-wide, partly explained by the increase in the ageing population and prevalence of diabetes[3]. In Denmark, the prevalence of CKD in the population is 4-8% depending on the applied algorithm[4]. CKD is a devastating disease both due to the risk of kidney failure and thereby the need for dialysis or transplantation, but also because the presence of CKD increases the risk of bone fracture, cardiovascular disease and mortality[2,5].

Disturbances in the mineral metabolism, including hyperphosphatemia and hyperparathyroidism develops as kidney function declines. These disturbances are closely related to the increased risk of bone and cardiovascular disease, and this relation has been gathered since 2009 in the clinical entity named Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)[1,6].

The bone pathology in patients with CKD, named renal osteodystrophy, can be classified by the TMV classification. The TMV classification describes the bone Turnover, the bone Mineralization and the bone Volume, which may all be disturbed in renal osteodystrophy[7].

Per see, disturbances in the bone pathology, especially in the bone turnover is considered harmful to the bone strength[8]. However, **no studies have addressed if disturbances in the bone turnover increases the risk of bone fracture**. This is the primary aim of the present study.

The golden standard for description of bone turnover is a bone biopsy. However, bone turnover markers may describe the bone turnover with a reasonable validity[9,10], and will be used in the present study to describe the turnover, as bone biopsy is not considered feasible in 1000 patients.

Especially, the low bone turnover has been a frightened condition as former studies have found an association between low bone turnover and progression of vascular calcification[11]. However, these were executed when treatment with active vitamin D and calcium were more aggressive than today. Treatments that may also affect the vascular calcification. Therefore**,** it is uncertain if low bone turnover predicts cardiovascular disease. This will also be explored in the present study.

Bone and cardiovascular disease often co-occur in patients with CKD. Preclinical and clinical studies has suggested a bone vascular tissue crosstalk in CKD that may be a mediator of the high risk of fracture and cardiovascular events in patients with CKD[12,13]. In the present study, it will be possible to explore how these factors, including sclerostin, Dkk-1, and Activin A, associate with changes in bone mineral density (BMD) and future fracture and cardiovascular disease.

Sarcopenia is an age-related disease characterized by a progressive decline in muscle function and mass [14]. Sarcopenia is associated with numerous adverse health outcomes in the general population, including increased risk of falls, fractures, and mortality [15]. Low BMD predicts an increased risk of fracture in the general population as well as in patients with CKD [6]. A few studies have found an association between osteoporosis and sarcopenia in patients with CKD [16]**.** This association between bone fragility and sarcopenia may be due to common risk factors such as age, sex, and malnutrition [17], but increasing evidence points towards an interaction between muscles and bone, giving rise to

the uniting term osteosarcopenia [18,19]. The present study will explore if sarcopenia predicts decline in BMD and future fracture.

Patients with CKD are often put on a strict diet to reduce their intake of phosphorous, potassium, sodium and protein. In theory, these dietary restrictions may in turn cause malnutrition, sarcopenia and increased risk of fall and fracture. Especially, the reduced calcium intake due to phosphorous restriction have been speculated to impact on the bone quality[20]. This study will determine the habitual dietary intake in patients with CKD4-5 and explore the association with bone quantity and sarcopenia.

A novel urine acid/base-score (calculated on the basis of urine pH and urine ammonium) assesses the renal tubular capacity for acid excretion and the degree of subclinical acid retention. This disease marker has been found to be largely independent of traditional kidney disease markers and robustly associated with CKD progression and incident ESKD in CKD stage 3-4 patients[21]. This study will determine the association between the subclinical acid retention and clinical outcomes.

4. Research questions

The primary research question is:

Does low bone turnover increase the future risk of fracture in patients with CKD?

Bone turnover will be quantified as bone turnover markers (described in section 7.6).

The 0-hypothesis is that low bone turnover does not increase the risk of future fracture in patients with CKD.

This prospective cohort study will provide broad insight into several aspects of CKD-MBD. Other future research questions can be addressed within this cohort study and will therefore provide valuable insight into different aspects of CKD-MBD.

<u>Bone</u>

1) Do bone turnover associate with decline in BMD?
2) Do bone turnover associate with increased risk of cardiovascular events?

3) Do disturbances in the mineral metabolism associate with the presence and progression of osteoporosis (presence of osteoporosis defined as T-score < -2,5 and progression defined as decreasing bone density measured with DEXA-scan)?
4) Do vascular derived biomarkers associate with decline in BMD and increased risk of cardiovascular events?
5) Does progression of osteoporosis associate with progression of CKD and cardiovascular events?
6) Does the bone phenotype and fracture risk differ between patients with and without diabetes?
7) Do bone turnover associate with novel circulating CKD-MBD biomarkers including Wnt- and TGF-β-signaling factors?
8) Do systemic and urinary markers of acid/base balance (measured as pH in blood and urine) associate with decline in BMD, increased risk of fractures or cardiovascular events?

For detailed description of measure of biomarkers measured in this trial, see section 7.6.

Sarcopenia

Does sarcopenia increase the risk of decline in BMD and future fracture and cardiovascular disease?

1) Does sarcopenia associate with low physical activity?
2) Does sarcopenia associate with a specific bone phenotype?
3) Do systemic and urinary markers of acid/base balance associate with sarcopenia?

Diet

1) Does low dietary calcium intake associate with low BMD and decline in BMD?
2) Does low dietary phosphate intake associate with low BMD and decline in BMD?
3) Does low dietary intake of protein associate with low muscle mass and strength?
4) Does a high dietary acid load associate with low muscle mass and strength?
5) Does high dietary potassium intake from fruit and vegetables induce hyperkalemia?
6) Does low dietary phosphorus intake associate with cardiovascular disease?
7) Does sodium intake and urinary sodium excretion associate with the progression of CKD and cardiovascular disease?
8) Does the source of protein (vegetarian versus animal) intake affect albuminuria?
9) Does the diet and acid production (pH in urine) associate with the progression of CKD

10) Does the source of phosphate (food or additive) affect the urinary excretion?
11) Does the balance between the dietary calcium and phosphate intake and the urinary excretion associate with the eGFR?
12) Does the product of p-calcium and p-phosphate associate with the eGFR?
13) How do the intake of phosphate associate with the intake of calcium

5. Outcomes

Primary outcome

The primary outcome is the difference in time to first fracture between patients with normal bone turnover and low bone turnover based on bone turnover markers at baseline.

Design

This is a prospective cohort study. Patients will be characterized at baseline and reassessed after 3 years. Bone fractures, cardiovascular events, progression of kidney disease, end-stage kidney disease and death will be collected through linkage with registries during follow-up (see section 11). The follow-up will continue until death or end of approvals.

6. Study population

The study will include 1000 patients with chronic kidney disease. The patients will be recruited from the outpatient clinic at the Department of Nephrology at Herlev Hospital.

6.1 Inclusion criteria

○ Age ≥18 years
○ CKD stage 4-5nonD (eGFR ≤ 29 ml/min) according to KDIGO (Kidney Disease Improving Global Outcome) definition[22].

6.2 Exclusion criteria

None

7. Study procedures

The procedures are summarized in **Table 1.**

7.1 Informed consent

Patients eligible for the study are identified with the help of the treatment-responsible staff at the outpatient clinic at department of Nephrology, Herlev Hospital. The outpatient clinic has ~8000 patients of which 1500 have an eGFR< 30 ml/min/1.73m2. Information about civil registration number, phone number, and CKD-stage is provided by the treatment-responsible staff and passed on to the study investigator prior to consent. Data used for screening patients will be from 0 to 10 years old, according on how long time the patient has been followed in our outpatient clinic. This information is used for identifying possible participants and for recruitment. Eligible patients will be invited to participate via a letter sent to them or during one of their ordinary visits at the outpatient clinic, where the written information is provided. Those who receive a letter will, if they don't contact us within 2 weeks, receive a follow-up phone call from us. If patients so desire, they can make a later appointment with the site investigator after having received written information about the trial. They are informed that they can bring one other person at this later appointment, and at that appointment they are once more verbally informed about the trial. The appointment takes place in a calm and undisturbed room in the outpatient clinic, with appropriate time for information and questions. After the meeting the patients may deliberate on the study participation for up to seven days. If the subjects decide to participate in the study, the written informed consent must be collected and signed before any study activity can take place. It is only possible to participate in the study if the subject is capable to give written consent. The patients will be informed that they at any time during the study may withdraw their informed consent with no consequence to their present or future treatment. If significant changes to the study are made, or if new risks associated with the study come to our knowledge, the participants will be informed of this, and they will be asked to renew their written informed consent.

7.2 Consent for long-term storage of blood samples in biobank and access to source data

Each patient will also be asked to give a separate consent to have their surplus materials included in a biobank, where samples will be stored until 1/8-2050 and then it will be destroyed. The subjects can participate in the study without their samples stored in the biobank for 25 years.
Permission to gain access to source data/documents (including medical records) regarding the

participants will be collected from the subjects in writing. They will also give consent to, that the investigator can obtain access to all relevant documents and records if inspections from different regulatory authorities or Ethics Committees are performed.

7.3 Subject ID number

All subjects enrolled must be identifiable in a pseudoanonymized form. All data will be registered in RedCap where a study ID number is given to the patient at the first visit.

7.4 Demographic data, medical history and medication

Date of birth and gender will be registered from medical records. Height and weight will be measured during visits., We will ask participants about ethnic origin/race, alcohol and smoking habits, eating habits, fall within the last 2 years, previous bone fractures, previous treatment with medicine containing steroid, current consumption of vitamin D, calcium, vitamin K, and proton pump inhibitors as well as their height at the age of 18 if this is known. The reason to ask for ethnicity is because of the possible effect on endpoints, we therefore wish to correct for ethnicity in the analysis.

Medical history and present disease are registered. Information of the above will be obtained from the participating subject and from their medical records and it will be recorded at baseline and at 3 years follow-up. Demographic and medical data is collected from medical records to be able to describe the cohort characteristics as it is known that a broad palette of characteristics affects our endpoints of interest. The informed consent from the participant will give investigators direct access to the above mentioned information.

Medication at baseline and at 3 years follow-up are registered.

7.5 Vital signs and physical examination

Height, weight, hip and waist circumference, blood pressure, and heart rate will be measured with validated automated devices at baseline and at 3 years follow-up.

7.6 Blood and urine samples

Blood samples are collected from all participants using standardised vein puncture techniques. 20 ml of blood is collected for routine analysis at baseline and after 3 years of follow-up: creatinine,

urea, ionized calcium, phosphate, magnesium, PTH, 25OH vitamin D, totalCO2, bicarbonate, sodium, potassium, urate, haemoglobin, albumin. These blood samples are analysed immediately by Department of Clinical Biochemistry.

Participants are instructed to collect a 24-hour urine at baseline for calcium, phosphate, magnesium, sodium, urea, acid/base parameters (ammonium and pH), creatinine and albumin analyses.

Extra 8 ml of plasma and 8 ml of serum will be collected at baseline and 3 years follow-up. These will be frozen at minimum -70°C and kept in the research biobank so that they can be analysed in batches. Bone turnover markers, osteocalcin, RANKL, OPG, Klotho, FGF23, wnt signalling factors including sclerostin and Dkk-1, TGFβ signalling factors including Activin A, myokines, adipokines, osteopontin, MGP, T50, fetuin A and CPPs, inflammation markers (such as IL-6, TNF-α), endothelial markers (i.e. VCAM, ICAM) are planned to be determined. The remaining material will be destroyed after all analyses have been performed and no later than 1/8-2035.

For future research further blood samples consisting of 8 ml serum, 10 ml EDTA-plasma, 6 mL heparin-plasma, buffycoat 2 ml, urine 4 ml will be collected and frozen at minimum -70°C for future research and kept for up to 25 years (1/8-2050).

7.7 DEXA scan

DEXA scans are performed on all participants at baseline and after 3 years follow-up. The DEXA scan estimates body composition, bone mineral density and vertebral fractures with a whole-body scan.

DEXA provides estimates of three compartments in the body composition: fat mass (FM), fat free mass (FFM), total bone mass (BMC). Appendicular lean mass (ALM) is defined as the sum of lean soft tissue from the arms and legs. Relative ALM is acquired by normalizing ALM to height to account for allometric differences in body size.

The content of calcium in the bones are assessed by the amount of calcium compared to the measured area in g/cm^2.The scan of the lumbar spine and the hips are performed while the subject is lying down, while the scan of the forearms is performed while sitting. The scan can be performed with clothes on, if the clothes does not contain any metal. The T- and Z-scores are calculated. Radiation from one DEXA-scan varies from 3 to 30 microsievert.

VFA is a way to assess fractures in columna thoracolumbalis using a DEXA scan. The VFA visualises the different vertebras, including a possible deformation of the vertebras. The radiation from one VFA is approximately 3 microsievert.

7.8 Dietary assessment

To assess the patients' weekly intake of vegetables, animal products, and sodium the participants must fill in two questionnaires (named "salt screener", "proteinscreener").

Additionally, in a subgroup of 50 patients, dietary intake with special emphasize on intake of calcium and phosphate will be assessed using a 24-hour recall based on patient-provided meal photographs. The patients will be instructed at visit 2 by an authorized clinical dietitian to photograph all meals and beverages consumed during a 24-hour period. At the following visit 2a a 24-hour recall will be conducted, during which the dietitian will review the photographs together with the patient. The patient will be instructed to fill in a 72-hour dietary diary.

7.9 Muscle strength and function

The hand grip strength will be assessed by a JAMAR meter. The muscle function will be evaluated by sit to stand test and 10 m-walk test. The body composition will be measured by bioimpedances. These will be performed at baseline and 3 years follow-up.

7.10 Questionnaires

Participants will be invited to fill in questionnaires at baseline:

SARC-F: screening tool for sarcopenia

KDQOLSF1.3: Quality of life assessment

Physical Activity Scale 2 (PAS-2): self-estimated physical activity

Proteinscreener: Assessment of intake of protein

Saltscreener: Assessment of intake of salt

The questionnaires will be sent through RedCap to e-boks.

7.11 Biobanks

2 biobanks are being established: one research biobank in order to analyse samples at the same time, and one future biobank for future research.

For the research biobank 8 ml of plasma,8 ml of serum and 10 ml urine will be collected at baseline. Samples from the research biobank will be destroyed no later than 1/8-2035, because it is expected to take years to include all participants. Residuals will afterwards be transferred to the biobank for future research if the participant has signed the informed consent regarding this.

For future research 26 ml blood (8 ml serum, 10 ml EDTA-plasma, 6 mL heparin-plasma, buffycoat 2 ml) and 4 ml urine 4 ml will be collected. Biobank with samples for future research will be kept up to 25 years, afterwards all leftovers will be destroyed. If they have not signed this consent, the leftovers from research biobank will be destroyed according to the participating laboratories standard procedure.

Table 1 | Visit Schedule

Visit Time	V0 < -6 mo	V1 -6 mo to -3 days	V2 0	V2a +2 to + 30 days	V3 + 30-42 mo
Information meeting	x				
Sign informed consent		x			
Preparation for 24 h urine		x			
Demographics			x		
Vitals			x		x
Dietary substudy			x	x	
Blood samples:					
routine			x		x

research biobank			x		x
future research biobank			x		x
24 hour urine sample:					
routine			x		
research biobank			x		
future research biobank			x		
DEXA			x		x
Hand grip, STS and 6 m-walk			x		x
Questionnaires			x		

8. Data management

A RedCap database will be established, in which all data will be registered. Data will be stored for 25 years, after which they will be anonymized.
All data are stored securely and only accessible for authorized personnel and trial staff. The trial staff will ensure that the subject's confidentiality is maintained.

8.1 Information from medical records

Information of parameters describing inclusion and exclusion criteria will be given from the treatment responsible doctor to the researcher in order to identify possible participants. These are from the medical records in the outpatient. When a subject has signed informed consent and has entered the trial, information about comorbidities and medication will be recorded from the medical record. The informed consent will give the investigator, and supervisory bodies access to look into the patient file in order to collect data and control the quality of data and monitor data. The study will be in compliance with "Databeskyttelsesloven" and will only be initiated after approval from "Videnscenter for Dataanmeldelser, RegionH, Denmark".

8.2 Case Report Form

An electronic CRF in RedCap is provided, and all data related to this study will be registered in it. This will provide the basis for a central database stored in coded form according to the rules of the

Danish Data Protection Agency. The CRF is to be completed by the study nurse or by the investigator at the time of the subjects visit to the clinic.

9. Statistical evaluation

Analysis of the primary endpoint will be performed after 200 fractures have occurred. The difference in time to first fracture will be analyzed by Cox proportional hazards model. Hazard ratios will be given with 95 % confidence intervals and p-values

Baseline characteristics will be presented with appropriate averages and measures of dispersion according to their distribution.

Continuous outcomes will be presented as graphs of mean and standard error of the mean at each time point. Continuous outcomes with non-normal distribution will be transformed to obtain normality before analysis. For outcomes with a baseline and a single follow-up measurement, comparison between treatment groups will be performed by ANCOVA, with adjustment for the baseline value. Outcomes with baseline and multiple post randomization measurements will be compared as baseline adjusted mean follow-up values using a mixed model repeated measures approach. Categorical outcomes will be compared by Chi^2-test. Hypothesis testing will use a 2-sided p-value to confirm or reject the null hypothesis. A p-value less than 0.05 is considered statistically significant.

10. Sample size/power calculation

The incidence of any first fracture is compared between patients with low and non-low turnover as a time to event analyses. The prevalence of low-turnover is expected to be 30%[9].

An annual incidence of fracture (proximal humerus, forearm, pelvis and hip) of 2 % is expected in the whole cohort[23]. To be able to detect a 40 % difference in the incidence of fracture (HR 0.6) in the patients without low turnover bone disease compared to patients with non-low turnover bone disease during 10 years of follow-up, and with a drop out of 20 % a total of 1000 participants will be included (β=0.20; α=0.05). The number of events will be monitored, and the sample size may be adjusted according to the incidence of fractures.

The dietary sub study is an exploratory and descriptive study with 50 participants.

11. End of study

When 1000 participants have been included the inclusion will stop. All included participants will be followed in the Danish registries (Landspatientregisteret, lægemiddelstatistikregisteret, dødsårsagsregisteret) until death or end of study which is expected to be after 25 years of follow-up.

12. Research biobank

A research biobank will be established. This biobank will store certain blood samples at minimum -70°C that needs to be analysed at the same time in order to avoid inter-assay variation. In the standard informed consent form, they will also sign that they give their consent to have some of their blood stored in this research biobank. It is not possible to decline and still participate in the study. From this biobank we will analyse biochemical markers related to this study and described in this protocol. Samples from the research biobank will be destroyed no later than 1/8-2035 or transferred to the biobank for future research if the participant has signed the informed consent regarding this.

13. Future biobank

A biobank for future research in bone disease in patients with CKD will be established at Herlev Hospital. This biobank will store blood samples and urine samples in coded form at minimum -70°C for future analysis. Each subject will be asked to give a separate consent to have their surplus material stored in this biobank, and subjects who decline this is still able to be part of the study. Samples will be stored until 1/8-2050 and after that it will be destroyed, unless dispensation from this has been provided. Additional analyses on these blood and urine samples will only be performed after approval by the Ethics Committee System on Biomedical Research. Blood and urine samples for future research will stored according to local legislation (*Databeskyttelsesforordningen)*.

14. Ethical considerations

The trial is investigator-initiated by Ditte Hansen and will not be initiated before approval from the local scientific ethics committee. The trial will be conducted according to local legislation (*Databeskyttelsesloven, Databeskyttelsesforordningen* and *Sundhedsloven*) and Declaration of Helsinki 2013.

CKD puts patients at high risk of cardiovascular and bone disease. This cohort will provide important information regarding diagnosis and prognosis for this condition. The participants will have their bone and dietary intake described in depth, which may be an advantage for each individual. The participants may not have any direct advantage of the results of the overall study, but provide information for improvement of diagnosis, prognostication and treatment of future patients with CKD.

Patients in the dietary-assessment subgroup will be offered a 1-hour consultation with an authorized dietitian. During the session the patients will get a detailed registration of their calcium and phosphate intake and will gain insight into common dietary phosphate sources. Participants will have the opportunity to ask questions related to diet and kidney disease.

14.1 Screening

The study will be streamlined and integrated as much as possible into the usual care to reduce the burden on the participants and study staff.

We expect to screen 1500 patients to be able to include 1000 participants in our study. See section 7.1 for information given to the researchers before consent.

14.2 Risk and discomfort for the patient

Blood samples will be drawn using standard sterile technique in a peripheral vein. The potential risks and discomforts in association to this is pain, hematoma, rarely an infection. A total of approximately 124 ml will be drawn over a 3-year period, maximally 62 ml at once. In section 7.6 is described specific analyses made on blood samples. There will be taken the same amount of blood as in the clinic (20 ml per visit) added with 42 ml to biobanks. As comparison, a blood donor donates 500 ml of blood at a time. The subjects undergo DEXA scans and VFA of columna 2 times. The known risk for the patient in relation to these scanning techniques is radiation. The radiation dose from one DEXA scan varies from 3-30 μSv, corresponding to <2 weeks of background radiation.

15. Financing and insurance

15.1 Financing

Neither the investigators nor the research group related to this study have any financial interests in the execution or the results of this study. Funding will be sought from national and international funds. Participants and the local scientific ethics committee will be informed as funding is secured. Those who support the study with funding will have no influence on the setup of the study, the interpretation of or the publication of data. Patients will not receive any financial compensation for their participation.

15.2 Insurance

If, against expectations, any harm should happen, patients will be covered according to current law on patient-insurance.

16. Publication

The results or partial results of the study will be written in one or more manuscripts with the purpose to be published in one or more international peer-reviewed journals. Both negative, neutral, inconclusive, and positive results will be published as quick as possible, academically sound and in accordance with law on the processing of personal data. Ditte Hansen, professor MD PhD, will be last author on publications of the main results. Authorships will be granted any persons who have contributed to the publications according to the Vancouver Guidelines.

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