The Effect of REgulation of PArathyroId hoRmone in patients with Chronic Kidney Disease to investigate the change in bone mineral density

(Biskjoldbruskkirtelhormon og knogletæthed hos patienter med kronisk nyresygdom)

The REPAIR-CKD trial

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Content

Purpose

The purpose of The REPAIR-CKD trial is to determine if treatment of hyperparathyroidism improves the bone mineral density in patients with chronic kidney disease.

During this trial it will also be evaluated if it is feasible to obtain a difference in PTH levels when targeting two different levels of PTH.

Further this trial will explore if a difference in PTH influences on arterial stiffness, muscle mass, muscle function, bone histology and health related quality of life.

Background

The prevalence of chronic kidney disease (CKD) is estimated to afflict 10 % of the adult population, and it is increasing world-wide(1). CKD is a devastating disease 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(2–4).

Parathyroid hormone (PTH) is a peptide hormone produced by the parathyroid glands(5). The main function of PTH is to regulate mineral metabolism, including the calcium and phosphate homeostasis(6). PTH increases as the kidney function declines, and at end stage kidney disease almost all patients have disturbances in the mineral metabolism(7,8). Treatment with activated vitamin D, phosphate binder and calcium supplementation has been used for more than 30 years to suppress hyperparathyroidism and keep calcium and phosphate within the normal range. Later calcimetics has been introduced as a treatment for secondary hyperparathyroidism(9).

The risk of bone fracture is increased in patients with CKD and the risk increases as the kidney function declines(10,11). A bone fracture leads to a direct burden on the individual. In addition, the

risk of complications after a bone fracture is higher in the CKD population compared to the general population(10,12). A fracture also constitutes a significant cost for the society(13). The increased risk of fracture in patients with CKD is associated to the presence of hyperparathyroidism(14).

Bone mineral density (BMD) assessed by dual energy x-ray (DXA) scan is a highly used modality to diagnose osteoporosis and future fracture risk in the general population(15). Bone mineral density associates with the risk of future fracture in patients with CKD(16,17). In patients with CKD there is an association between decreasing eGFR and both low BMD and future fracture risk (18). It is unknown how elevated PTH associates with BMD and its changes at different stages of CKD, and it is unknown if treatment of hyperparathyroidism influence on BMD and fracture risk in patients with CKD.

The risk of cardiovascular mortality, coronary heart disease, heart failure, stroke and peripheral arterial disease increase as the kidney function declines(19,20). Elevated PTH associates with an increased risk of cardiovascular disease(14). However, hyperparathyroidism is tightly connected to the general disturbances in the mineral metabolism in CKD, i.e. hyperphosphatemia and elevated FGF-23, which associate with an increased risk of cardiovascular disease and mortality(21,22). Therefore, it is questioned if PTH is directly involved in the pathogenesis of cardiovascular disease, or if the increased risk of cardiovascular disease could be caused by other factors involved in the mineral metabolism(23). One way to approach precursors of vascular disease is measuring vascular stiffness with pulse wave velocity which is associated with cardiovascular outcomes in patients with CKD(24).

The active circulating form of vitamin D is 1,25 dihydroxy vitamin D (calcitriol). The level of calcitriol is regulated by the activity of the 1α hydroxylase enzyme located in the kidney. The 1α hydroxylase enzyme hydroxylate 25-hydroxy vitamin D at the 1-position(25). As kidney function declines the activity of 1α hydroxylase is reduced and thereby the circulating level of calcitriol is reduced(26). The reduced level of calcitriol, together with hypocalcaemia and hyperphosphatemia, leads to secondary hyperparathyroidism(27). Activated vitamin D is given to patients with hyperparathyroidism to try lowering PTH(28). In a randomized placebo-controlled trial with 36 patients with CKD G3-5 the intervention group were treated with active vitamin D, which resulted in a difference in BMD by +4.2% in the spine compared to controls after 18 months ($P< 0.05$) (29). No clinical trials have aimed to explore the influence of targeting different levels of PTH and the influence on bone mineral density or bone fracture in patients with CKD.

Two randomized placebo-controlled trials aimed to address effect of 1 year of active vitamin D treatment on the left ventricular mass, a surrogate endpoint for development of heart failure. No difference between the treatment groups was found in any of the trials(30,31). Cohort studies in dialysis patients have found increased survival in patients treated with active vitamin D, but the result could be biased having the design in mind(32). One Japanese randomized controlled trial compared alfacalcidol with placebo in 976 patients on dialysis(33). Of importance, not all the included participants did have hyperparathyroidism. No difference was found in fatal and non-fatal cardiovascular events, additionally no difference was found in risk of fracture during the study. If this finding would have differed in patients with hyperparathyroidism or in patients with earlier stages of kidney disease and thereby preventable progression of vascular calcification, remains to be determined.

Treatment with active vitamin D, phosphate binders and calcimetics has been used for patients with CKD for decades. Recommendations regarding the appropriate dose and PTH target for different stages of CKD has varied during years and between guidelines(34,35), reflecting the lack of randomized clinical trials with clinical important end points (**BOX 1**).

BOX 1 | Guideline recommendations for research

Multicenter RCTs should be conducted in children and adults to determine the benefits or harms of calcitriol or vitamin D analogs in patients with CKD G3a to G5; patient-level outcomes including falls, fractures, sarcopenia, muscle strength, physical function, progression to end-stage kidney disease, cardiovascular events, hospitalizations, and mortality should be assessed. …... Studies should also include patients with more severe SHPT and should determine the impact of reducing PTH to different target levels, such as the normal range versus higher levels.

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

In people with hyperparathyroidism secondary to CKD, does treatment with vitamin D or vitamin D analogues improve patient-related outcomes.

NICE guidelines 2021

In patients with CKD G3b-5, it is currently recommended to monitor the PTH every 3-6 month(3). As more than 50 % of the patients have elevated PTH already at CKD G3b, it is an everyday

consideration for the clinician if the patients should be treated to reduce PTH. This is both time- and cost consuming. At present, there is no evidence to advise if secondary hyperparathyroidism should be treated in patients with CKD.

To improve our knowledge about when secondary hyperparathyroidism should be treated, we want to conduct a randomized clinical trial with one group of patients being treated if PTH is elevated versus a second group of patients not being treated if PTH is elevated.

Hypothesis

We hypothesize that suppression of initially elevated PTH will improve BMD, arterial stiffness, muscle mass and muscle strength in patients with CKD.

Methods and Materials

Subjects will be recruited from the patient population in the outpatient clinic at the Department of Nephrology at Herlev and Gentofte Hospital, Herlev, Denmark.

Study population

Inclusion criteria (all four needs to apply)

1. ≥50 years of age at screening
2. CKD G4-5nonD (eGFR < 30 mL/min/1.73m^2) based on local laboratory assessment of serum creatinine and eGFR estimated by the CKD-EPI formula)
3. Plasma PTH > upper normal limit of local laboratory reference range (> 8,5µmol/L) and/or treated with active vitamin D (Alphacalcidol) or calcimetics (Cinacalcet) initially
4. Written informed consent

Exclusion criteria

1. Patients who have received a kidney transplant
2. Patients receiving treatment with specific anti-osteoporosis medication (denosumab/bisphosphonates) (because of the profound effect on calcium/phosphate fluxes and BMD)

Withdrawal from intervention but continued follow-up (included in intention-to-treat analysis)

1. Withdrawal of consent
2. Kidney transplantation

3. Parathyroidectomy
4. Necessity to initiate dialysis treatment

Patients may withdraw from both intervention and follow-up at any time if desired.

Study design

The REPAIR-CKD trial will be an investigator-initiated pragmatic randomized controlled clinical trial. Included patients will be randomized 1:1 into one of two treatment arms with different targets levels for plasma-PTH: A liberal PTH target (< 5 x upper normal limit = 42,5 µmol/L) or an intensive PTH target (within interval of lower and upper normal limits = 2,0 – 8,5 µmol/L) (**Figure 1**)**.** The cut-off for the liberal PTH target (<5 x upper normal limit) was discussed in the national CKD-MBD group. It is chosen to allow the clinician initiate treatment if PTH reaches unusually high levels, no studies have focussed on PTH-targets before, consequently the cut-off is chosen as part of the pragmatic design.

The trial will also pilot the feasibility to obtain a difference in the PTH levels between treatment groups.

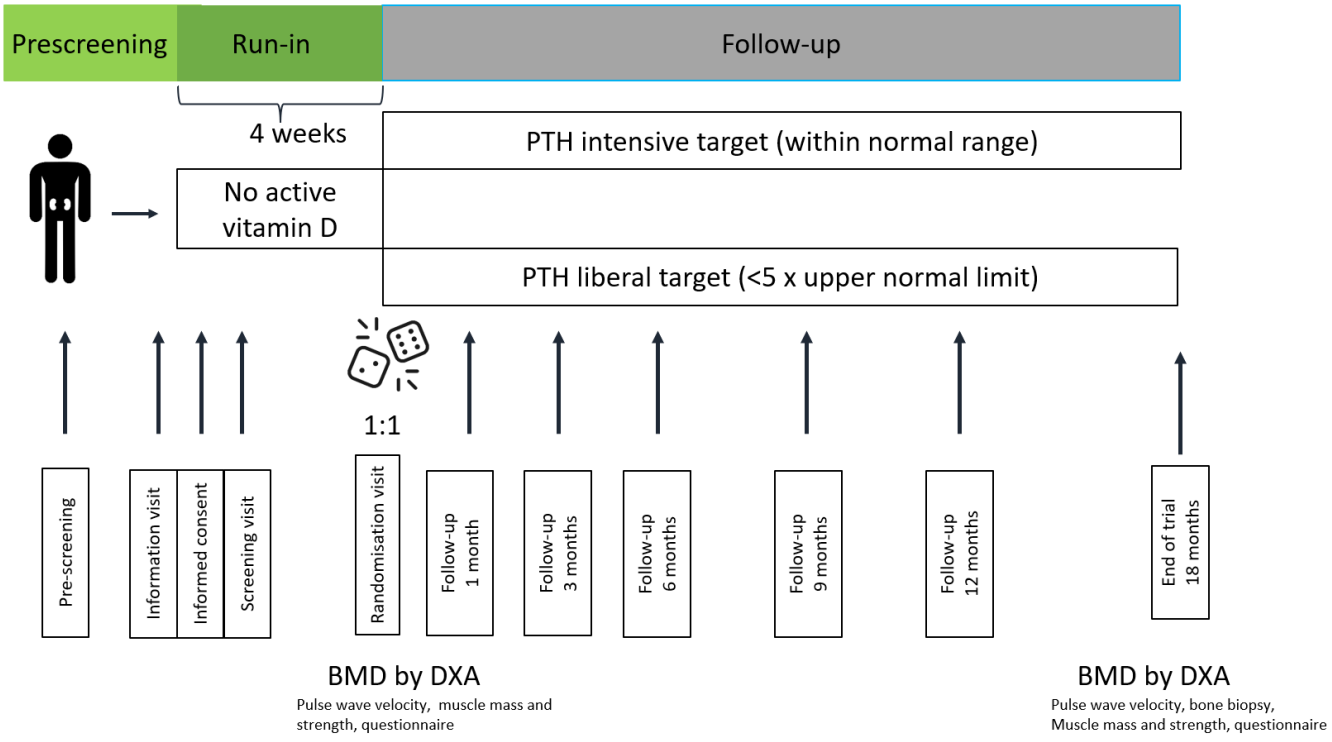

Figure 1. Visit overview.

Sample size

The primary outcome will be difference in the change in total hip BMD between treatment groups.

In an observational study, the decline in total hip BMD (g/cm^2) was -1.19%/year (men) and -1.51%/year (women) The decline in men is chosen for a conservative estimate (36). In the dialysis population, the standard deviation (SD) of the one-year decline in BMD is +/- 5.2% (37). The variance in the BMD change in dialysis patients is expected to be higher than in the CKD population, and therefore this is considered a conservative estimate. Based on these observations the expected decline in BMD in the liberal target group during 18 months is -1.8% (5.2%).

In a previous trial, alendronate was able to increase BMD in total hip by 2.8% during the first year of treatment and 3.4% during 2 years treatment, and thus to increase BMD by 3.1% in 18 months (38). We expect to obtain a similar effect in the intensive target group.

A sample size of 70 participants is estimated (β=0.10; α=0.05 (two-sided), drop out 20 % during the study) to detect a difference of 4.9 % change in total hip BMD (effect size) during 18 months.

To ensure that the trial can also provide information about the other fields of interest, we did some statistical considerations about these as well. A minimal relevant difference in the level of PTH after 18 months of intervention is expected to be a difference in PTH of 0.5 times the upper limit of normal range (8.5 µmol/L (Atellica IM PTH)). PTH has a skewed distribution and thus log transformed to obtain normality. In a population of patients with CKD G4-5 the mean and standard deviation of the logPTH was 1.191 (0.380) (own data, not published). To obtain a difference of 4.25 µmol/L in PTH = logPTH of 0.628 ((β=0.10; α=0.05) a sample size of 22 participants is estimated (including drop-out margin of 20%). Based on former studies the sample size should be sufficient to demonstrate a difference of 1 m/s in pulse wave velocity which is considered a difference of clinical relevance for future cardiovascular events(39).

Interventions

The trial is estimated to run for 24 months, as patients will be included during a 6-months period following 18 months follow-up. Following inclusion there will be a 4 weeks run-in period where patients will not be treated with active vitamin D or calcimetics. After run-in patients will be

randomized to either a liberal PTH target (< 5 x upper normal limit = 42,5 µmol/L) or an intensive PTH target (within interval of lower and upper normal limits = 2,0 – 8,5 µmol/L). In the intensive PTH target group, treatment will be initiated as soon as the PTH rise above the upper limit of normal. In the liberal PTH target group, treatment will not be initiated until PTH rise above five times the upper limit of normal.

PTH will be measured as intact PTH with Atellica IM PTH assay at Herlev Hospital laboratory (normal range 2,0 – 8,5 µmol/L).

Medications used for management of the disturbances in the mineral metabolism in CKD are native vitamin D, activated vitamin D, phosphate binders and calcimetics. As this is a pragmatic trial embedded in the clinic with usual care, these may be used after the run-in period according to the international guidelines to regulate PTH in the trial cohort (3). All medications for management of disturbances in the mineral metabolism will be registered and reported as part of results.

Study parameters

Baseline characteristics

Age, height, weight, sex, ethnicity(40), smoking status and alcohol use will be registered. Further comorbidity, medical history, biochemical data and medication (including native vitamin D, activated vitamin D, phosphate binders and/or calcimetics) will be collected from participants' medical record and interviews during the trial. The consent will allow the principal investigator, the sponsor and the sponsor's representatives, as well as regulatory authority, direct access to obtain information from the patient's medical records, including electronic records, in order to review information about the trial subject's health condition that is necessary for the conduct of the research project and for control purposes, including self-monitoring, quality control, and monitoring, which they are obligated to perform.

Blood samples

Standard blood samples will be drawn at initiation and month 1, 3, 6, 9, 12 and 18 to measure PTH, ionized calcium, phosphate, creatinine, eGFR, magnesium, haemoglobin, sodium and potassium. 25-hydroxy vitamin D will be measured at initiation and month 3, 9 and 18. Standard blood sample analyses will be run immediately at the local department of clinical biochemistry. Any remaining material after analysis will be destroyed.

For analyses of 1,25-dihydroxy vitamin D, fibroblast growth-factor 23 (FGF23), T50, TRAB5b, bone specific alkaline phosphatase, total alkaline phosphatase and iP1NP, blood samples will be taken at day 0 and at 18 months and stored in the research biobank. PTH will also be measured at in these samples. The biobank will contain samples at -80ºC and be analysed in bulk to minimize cost and intra-assay-variability. All residual samples therein will be destroyed after end of study (no later than 1/9-2027).

Volume of the standard blood samples at each visit is 16 ml. Further there will be drawn 14 ml at baseline visit and 18-months visit for the research biobank and 18 ml once for the biobank for future research (discussed in more details in p. 14 “Biobank for future research”). Maximal volume blood drawn at once is 48 ml (baseline visit). Total amount of blood drawn in the study will not exceed 200 ml.

DXA-scan

DXA-scan will be used to measure BMD (amount of calcium and phosphate per area in g/cm^2 followed by calculation of T-score) in lumbar spine, left hip (if not applicable, then right) and non-dominant forearm (if not with a fistula). Whole body scan will be performed to measure whole-body BMD and appendicular lean body mass as an approximation of muscle mass. Additionally, vertebral fracture assessment (VFA) will be performed to assess any fractures in lumbar spine. Efforts will be made to optimize that baseline and follow-up procedure will be performed by the same person to minimize interobserver variance. The research laboratory at Herlev Hospital has research staff and DXA-scan (Hologic Horizon, 2021-2022) for performing the measures. The above-mentioned procedures will be carried out after validation on a spine fantom performed daily and calibration of body composition takes place simultaneously (Refer to the Horizon User Guide (MAN-08072-002) for operating instructions). All patients included will have a DXA-scan at day 0 and at 18 months.

Bioimpedance

Body composition parameters, including segmental lean mass (arms, legs, trunk), skeletal muscle mass, fat-free mass, and body fat percentage, will be measured at baseline and 18 months follow-up by bioelectrical impedance analysis (BIA; multi-frequency InBody 570).

Pulse wave velocity

Pulse wave velocity will be assessed at day 0 and at 18 months by applanation tonometry with Sphygmocor. Pulse wave analysis is a non-invasive way of estimating to which extent peripheral reflection is augmenting central blood pressure. Pulse wave velocity is a direct measure of arterial stiffness. This procedure will be performed in accordance with a standard operating procedure and in accordance with guidelines from DaHS (Danish Hypertension Society). The Sphygmocor exists at the research laboratory at Herlev Hospital.

Muscle strength and function

Muscle strength and function will be assessed at day 0 and at 18 months by hand grip strength, 10 meter walk test, and sit-to-stand test. Hand grip strength will be measured by using a Jamar dynanometer (Sammons Preston Rolyn, Chicago, Illinois, USA). The procedure will take place with the patient sitting and will be measured three times in each arm performed with a pause for 45 seconds between each test. 10 meter walk test is done with stopwatch (timed to closest 0.1 second) and takes place in the corridor in the research laboratory at Herlev Hospital. Walking speed will be calculated as meter/second. Sit-to-stand test is performed by observing and documenting how many times the patient is able to sit and stand within 30 seconds with crossed arms from a standardized chair.

Bone biopsy

All participants will be invited to have a bone biopsy performed at 18 months follow-up to explore how the intervention influences on bone histology. Tetracycline labelled bone biopsy is performed by a trained physician experienced in performing bone biopsies from the iliac crest after a standardised procedure. At randomisation, we will start with a single labelling of the bone with tetracycline, for us to be able to tell how the bone was at the time of randomisation. Before the biopsy procedure the bone is again labelled with tetracycline.

The bone biopsy is performed with local anaesthesia and a sterile technique, and the entire procedure takes approximately 30 minutes. After the procedure the patient will rest at the study site for approximately 2 hours. Before going home patients are also instructed on which pain medication they can take if needed. The size of the biopsy is 4,5 mm x 10-15 mm. The bone biopsy is kept in formalin and will be pseudo-anonymized before shipment to Odense University Hospital for analysis. This procedure will not be mandatory, as our experience shows that some patients are

hesitant about undergoing a bone biopsy. Therefore, we will not risk that some may choose not to participate in the trial due to this hesitation.

Questionnaire

Health related quality of life will be evaluated at initiation and after 18 months through questionnaire “Kidney Disease and Quality of Life” (KDQOL-SF1.3, Danish version). The questionnaires will be sent by e-mail or e-boks from the primary investigator to the participants. If an answer has not been received after 14 days a reminder will be e-mailed. If the questionnaire has not been answered 14 days after the reminder, the research team will contact the participant by phone and ask if they need assistance for the questionnaire by the site staff or by receiving it by ordinary mail.

Visit schedule

Visit / Procedure	Visit 1 - >30 days	Visit 2 - <30 days	Visit 3 Day 0	Visit 4 1 month	Visit 5 3 months	Visit 6 6 months	Visit 7 9 months	Visit 8 12 months	Visit 9 18 months
Information	X								
Sign informed consent		X							
Randomization			X						
Screening			X						
Baseline characteristics			X						
Comorbidities, medical history, medication			X						
Standard blood samples			X	X	X	X	X	X	X
25-hydroxy vitamin D			X		X		X		X
Research biobank samples			X						X
DXA-scan			X						X
Pulse wave velocity			X						X

Hand grip strength, 10 meter walk test and sit-to-stand			X						X
Questionnaire			X						X
Bone biopsy									X*
Adverse event collection			X	X	X	X	X	X	X

Table 1. Visit schedule. *indicates that it is optional.

For visit 4-8 there will only be taken blood samples with follow-up by phone to minimize time consume for both patient and the investigator. Patients with CKD4-5nonD are usually scheduled in the outpatients clinic 4 times annually, investigators will try to plan the study visits on the same days.

Biobank for future research

There will be established a biobank for future research consisting of 10 ml serum and 8 ml EDTA-plasma from each patient signing the separate informed consent regarding the biobank for future research. The biobank material will be pseudonymised and kept in a locked freezer at -80ºC. This is not mandatory for participating in the trial. Patients may at any time contact the primary investigator to have their plasma and serum destroyed. Analyses on the biobank material can only be performed after application and approval by the Ethics Committee System. Samples will be destroyed after 20 years.

Randomisation

Patients will be randomised in a 1:1 ratio to either the intensive PTH target group or the liberal PTH target group for an 18-month period. Randomisation will be performed within computer software.

Blinding

PTH is routinely measured in the clinic and blinding is not feasible as unblinding of the allocated treatment group will easily occur. The open-label design may influence the adherence, as the treating physician or the patient may favour a specific PTH target. It is therefore of great importance to monitor the adherence to the allocated treatment target through levels of PTH, and doctors as well as participants will be encouraged to comply.

The DXA-scan and analysis of this will be blinded, as the investigator performing the intervention will not perform the scans.

Efficacy endpoints

Primary endpoint:

Difference in % change in bone mineral density (BMD) between the treatment groups.

This is the generally accepted outcome for trials comparing treatment effects on BMD.

Secondary endpoints:

- Difference in follow-up BMD between treatment groups
- Difference in follow-up arterial stiffness between the treatment groups
- Differences in follow-up muscle mass between the treatment groups
- Differences in follow-up muscle function between the treatment groups
- Differences in bone histology between the treatment groups
- Differences in follow-up health-related quality of life between the treatment groups
- Differences in number of spinal fractures between the treatment groups

The feasibility to obtain a differential PTH level of at least 0.5 times the upper limit of normal between the two groups will be determined. During the piloting the number of withdrawals of consent and crossovers will be determined to improve the set-up, to increase retention and adherence and adjust the sample size estimation.

Adverse events

All serious adverse events (SAE) will be recorded during trial period. SAE is any case of death, life threatening event, persistent or significant disability, hospitalisation, prolongation of existing hospitalisation or treatment necessary to avoid the above and congenital anomaly/birth defect. It is the responsibility of the investigator to assess whether any SAE is with reasonable possibility causally related to the study intervention. Within 7 days after becoming a
ware of a SAE, the investigators will report these to the local scientific ethics committee. Once annually the primary investigator will report a summary of SAEs to the local scientific ethics committee.
All cases of hyper/hypocalcaemia and hyperphosphatemia will be registered as adverse events of interest.

Statistics

All included participants will be accounted for and presented in a CONSORT diagram.

Baseline characteristics will be presented as mean ± standard deviation or median and interquartile range, and number and percentages.

The primary endpoint % change in BMD during 18 months will be compared between groups with unpaired t-test.

This will be further explored by comparison of BMD after 18 months by ANCOVA adjusted for baseline BMD.

For secondary outcomes with a baseline and a single follow-up measurement, comparison between treatment groups will be performed by ANCOVA, adjusted for the baseline value. If more suitable, this analysis will be done with mixed effect model.

Secondary outcomes with baseline and multiple post-randomization measurements will be compared as baseline-adjusted follow-up values using a mixed model repeated measures approach.

Categorical outcomes will be compared by Chi^2-test. Continuous outcomes will be presented as graphs of means and standard error of the means at each time point. Continuous outcomes with non-normal distribution will be logarithmic transformed to obtain normality before analysis.

Two-sided P-values < 0.05 is considered statistically significant.

All data will be described including data-incompleteness as well as reasons for data-incompleteness. Imputation will be used, if reasonable, to manage data-incompleteness in the analyses.

Analyses will be run in R studio, SAS and STATA. A statistical analysis plan will be decided before data lock.

Time schedule

The study will not be initiated until approved by the local scientific ethics committee, expected in summer of 2025. Recruitment is expected to last 6 months followed by 18 months follow-up. The study period will last 18 months for each patient.

Rights and publication

Principal investigator Freja Stæhr Hassager, MD will coordinate the study. Freja Stæhr Hassager will be first author on any subsequent publications.

Ditte Hansen will be final author on any subsequent publications.

Authorship will be granted to any person who contribute to the subsequent publications according to the Vancouver Guidelines.

All results, either positive, negative or inconclusive, will be submitted for publication in peer-reviewed journals.

Ethics

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. Further, the trial will be registered at ClinicalTrials.gov before initiated. Since activated vitamin D, calcimetics and phosphate binders are already used to treat hyperparathyroidism and there is no evidence of the optimal PTH-target, the trial is not considered a drug study (correspondence with the Danish Medicines Agency, DMA, case number 2025030893) and will not be monitored by the Good Clinical Practice Unit.

Screening and inclusion

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.

The treating physician in the outpatient clinic at Department of Nephrology may pre-screen the patients for possible enrolment in the study. The pre-screening will involve patients in the outpatient clinic at the Department of Nephrology. Pre-screening will include access to information about age, status on kidney transplant, eGFR, PTH and medication in the patients' medical journal to clarify if patients meet inclusion criteria. Data used for screening patients will be from the time the patient is pre-screened and back to 2015. During trial period there will be pre-screened approximately 500 patients to include 70. The pre-screening process will make the clinicians deliver personal information (personal identification number and telephone number) to the primary investigator prior to the written consent.

Patients meeting the inclusion criteria will be contacted in one of two ways:

1) Treating physician giving short information to the patient in the outpatient clinic and the patient giving oral consent to be contacted at telephone by an investigator. Primary investigator will call the patient within 14 days after consent.
2) Recruitment letter: The patient will be contacted through e-boks where they will receive an invitation to participate in the trial. Within the letter there will be e-mail and phone number to primary investigator for them to contact. If the patient does not contact the primary investigator within 14 days after receiving the letter, primary investigator will call the patient to make sure they received and read the letter. Otherwise, primary investigator will give short information about the trial and encourage the patient to read the letter.

Regardless of the pre-screening method, if the patient desires to participate in the trial, an appointment with principal investigator for informing the patient will be scheduled. Such a meeting must take place in an undisturbed room and the patient may bring a family member or friend to aid in decision-making. The facilities for an undisturbed meeting is in place at the research department at Herlev Hospital. Written informed consent must be signed within 30 days after this meeting. Upon giving written informed consent, the study participants give permission to the study investigators to access the participants' health records to collect relevant information for the study.

Participation in this trial will be voluntary and participants may withdraw consent from intervention, follow-up and biobank for future research separately during the trial.

Risk for participants

Treatment of hyperparathyroidism has been performed for decades. Activated vitamin D, phosphate binders and calcimetics are all highly recognized treatments in patients with CKD. Participation in this trial does not provide the participants with any additional risk than the present everyday treatment which depends on the clinical decision by the individual physician.

Blood samples will be drawn from a peripheral vein using standard sterile technique which includes risk of discomfort, bleeding, hematoma and rarely infection.

The DXA-scan is performed without pain for the patient and does not require infusion of any contrast. DXA expose the participants to a low dose of radiation (3-15 μSv), corresponding to <1 week of background radiation (41,42).

Pulse wave velocity measurement using SphygmoCor is non-invasive and do not expose any risk to the patient.

Test of hand grip strength, 10 meter walk test and sit-to-stand test is not expected to add any risk of complications to the patients.

Bone biopsy from the iliac crest is an invasive procedure. The most common complication after the biopsy is pain, which usually disappears within a few days. The patient will be given paracetamol from the hospital after the procedure to use for the following days. 2-3 in 1000 patients experience hematoma, neuropathy or pain lasting for more than a week. Less than 1 in 1000 patients experience infection in the skin that required antibiotics. Extremely rarely (1 in 10.000) patients experience infection in the bone or fracture as complication to the procedure(43). Risk of complications is minimized by having a trained physician experienced in performing bone biopsies doing the biopsy. The treatment with tetracycline can provoke allergic reaction and gastrointestinal problems.

The future health related benefit for the patients with CKD is expected to balance the above-mentioned minimal risk added to the patients in the trial. Hopefully in the future we will be able to treat patients with CKD and hyperparathyroidism based upon evidence to lower risk of fractures.

If significant health-related findings about an included patient should be made, the patient will be informed, unless they have requested not to be informed. As the results from the trial are published the patients will also be informed of the results of the trial. Each patient will be given written contact information of the primary investigator if they wish to be given more detailed information regarding the trial. Subjects participating in the trial will be insured by the Patient Compensation Association (Patienterstatningen).

Data

Data on individual study participants will be kept in an electronic case report form (CRF, REDCap). Data from CRFs will be kept for 20 years and deleted afterwards.

Financing

The patients will not be paid for their participation in the trial.

The salary to primary investigator and additional expenses to analyses and publications is covered by funding by the Novo Nordisk Foundation (2.4 mio. kr) and the Augustinus Foundation (1.6 mio. kr.).. Salary to primary investigator is handled through the department.

The investigators do not have any conflicts of interest in this project.

Perspective

The presented project will increase the knowledge of how PTH influences on bone mineral density and arterial stiffness in patients with chronic kidney disease. It will inform a large-scale randomized trial exploring the influence of targeting PTH in patients with chronic kidney disease. The aim is to improve treatment of hyperparathyroidism, and to avoid cost in time and money monitoring and treating patients with chronic kidney disease if the treatment is useless.

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