The effect of multi-faceted intervention on osteoporosis and CKD-MBD

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Brief Title: Intervention on Osteoporosis and CKD-MBD

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STUDY SUMMARY

Title	The effect of multi-faceted intervention on osteoporosis and CKD-MBD
Methodology	Prospective interventional cohort study
Study Duration	Estimated duration for the main protocol is from January 1, 2020 to December 31, 2020.
Study Center(s)	Multi-center (National Taiwan University Hospital and National Taiwan University Hospital Chu-Tung Branch)
Objectives	To evaluate the effect of pharmacological therapy and behavioral interventions among patients with chronic kidney disease having risk of osteoporosis related fracture
Number of Subjects	60 subjects in a single arm
Diagnosis and Main Inclusion Criteria	Inclusion criteria 1. Age > 50 years 2. CKD stage 3-4, and eGFR >20 mL/min/1.73m^2 3. FRAX® screening threshold: risk of hip fracture (HF) and major osteoporotic fracture (MOF) (HF: men> 6%, women > 7%; MOF: men> 15%, women> 12.5%) Exclusion criteria 1. Unable to consent (e.g. dementia) 2. Have cancer under treatment 3. Have acute coronary syndrome (unstable angina, non-ST elevation myocardial infarction, ST-elevation myocardial infarction) or stroke in 3 months. 4. Limited cognitive or physical function for execute the intervention
Interventions	1. Pharmacological therapy for chronic kidney disease-mineral bone disorder and osteoporosis 2. Behavioral interventions including diet modification and exercise for bone and cardiovascular health
Statistical Methodology	Primary outcome: all-cause mortality, cardiovascular events, subsequent fracture rate, and fall rate Secondary outcome: biochemistry laboratory tests before and after multifaceted interventions

1 STUDY OBJECTIVES

1.1 Primary Objective

- Collect the baseline characteristics to screen for CKD-MBD and osteoporosis among CKD patients/ Deliver optimal care including pharmacological therapy and behavioral interventions for CKD, CKD-MBD, osteoporosis, and fragility fractures accordingly to the baseline characteristics.
- Primary outcomes are all-cause mortality, cardiovascular events, subsequent fracture rates, and fall rate.

1.2 Secondary Objectives

- Secondary outcomes are changes of biochemistry laboratory data before and after interventions (pharmacological therapy and behavioral interventions).

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Previous studies among CKD patients found the fracture incidence to progressively increase by 15.0, 20.5, 24.2, 31.2, and 46.3 per 1000 person-years for CKD stages 1 to 2, 3a, 3b, and 4, respectively[1]. The risk of fracture increases to 5 times higher in patients with an estimated glomerular filtration rate (eGFR) <15 versus >60 ml/min per 1.73 m^2). Patients with CKD and older than 65 years of age have a higher rate of fractures during 3-years of follow-up[2]. It would be an important issue to prevent skeletal fracture among older adults with CKD since fracture can cause higher mortality and health resource utilization and loss of quality of life.

Renal osteodystrophy is used previously to describe the histological changes of bone among CKD patients. However, these changes in mineral and bone metabolism were derived from dysregulation during renal function deterioration gradually. Therefore, the mineral and bone disorder associated with CKD is an evolving entity which caused abnormalities of mineral metabolism, bone turnover, and vascular calcification. The KDIGO CKD-MBD guideline suggests that a bone biopsy should be considered for patients with a presentation of bone pain or unexplained fracture[3]. A transiliac bone biopsy after tetracycline labeling is the gold-standard technique for diagnosis of CKD-MBD. However, this invasive measure might not be acceptable to many patients and only few centers have the expert histomorphometry analyzers[4]. In clinical practice, the primary osteoporosis is a more prevalent disease among older adults. The KDIGO CKD-MBD also suggested application of dual-energy x-ray absorptiometry (DXA) in evaluation the fracture risk among CKD patients[3]. In order to prevent fragility fracture, it would be reasonable to target abnormalities of mineral metabolism and primary osteoporosis. Further studies for CKD-MBD would be considered for those with unexplained factures or bone pain. Tools to evaluate osteoporosis and CKD-MBD are briefly described below.

Bone mineral density (BMD)

The relevance of bone mineral density as measured by dual-energy X-ray absorptiometry (DXA) is limited in CKD patients because of interference of scoliosis, osteoarthritis at the lumbar spine, and the presence of vascular or joint calcifications. However, BMD measurement was also recommended for older adults with CKD in the 2017 KDIGO guidelines which were supported by several studies[5].

FRAX®

The Fracture Risk Assessment Tool can be used to predict peripheral fractures in older patients with CKD stages 2 to 5. Clinical risk factors such as weight, height, prevalent fracture, family history of hip fracture, and steroid use are sufficient for 10-year prediction and are as efficient alone as together with hip BMD.

Serum biochemistry

Vitamin D sterols.

Circulating values of native vitamin D (25-hydroxyvitamin D [25OHD]) allow determination of vitamin D storage. But, the optimal circulating 25OHD level in CKD that protects against skeletal fractures is controversial. 2017 KDIGO guidelines recommend using the same 30 ng/ml cutoff value used for the CKD patient without dialysis.

Phosphate.

In previous study, serum phosphate levels are associated with higher fracture risk in both genders and in a subgroup of men with CKD[6]. Tubular reabsorption of phosphate (TRP) in patients with CKD stage 3 to 4 is an index of phosphaturic homeostatic mechanisms[7].

Parathyroid hormone.

PTH is the best surrogate biomarker for bone histology in CKD in clinical practice[8].

Other biomarkers of mineral metabolism, such as calcium, and total ALP, are used as surrogate markers of high- or low-turnover bone disease.

X-ray film.

Lumbosacral spine anterior-posterior (AP) and lateral view will be used to evaluate aorta calcification and spinal compression fractures.

2.2 Study Rationale

A prospective intervention study is purposed to investigate whether the optimal therapy targeting those with risk of fragility fracture risk and CKD would lead to the better outcomes. Patients with CKD stage 3-4 (eGFR 60-20mL/min/1.73m^2) are screened with FRAX®. If patients have high risk of osteoporotic fracture, they will be enrolled for serial examination and education to prevent complications of CKD and osteoporosis.

The primary outcomes are all-cause mortality, cardiovascular events, subsequent fracture rate, and fall rate. The secondary outcomes are changes of biochemistry laboratory data before and after interventions (pharmacological therapy and behavioral interventions).

3 STUDY DESIGN

The design is a pilot study with data collection through interviews, and medical records. There is one study arm: the intervention. A description of multi-faceted intervention on osteoporosis and CKD-MBD can be found in STUDY INTERVENTIONS. The pilot will take place at two primary clinical care practices in National Taiwan University Hospital and its Chu-Tung Branch in Taiwan. 60 patients will be enrolled and followed for up from January 1, 2020 to December 31, 2020 with interviews and medical record reviews. Participants will undergo a baseline and follow-up interview to collect patient reported baseline and outcome measures.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants will be enrolled at two physicians in National Taiwan University and its Chu-Tung Branch. The intervention patient population will involve adults (age older than 50) with chronic kidney disease stage 3 or 4. Participants will be enrolled and identified using the inclusion/exclusion criteria. The physicians have been trained to conduct clinical trials.

4.1 Inclusion Criteria

1. Age > 50 years
2. CKD stage 3-4, and eGFR >20 mL/min/1.73m^2
3. FRAX® screening: risk of hip fracture (HF) and major osteoporotic fracture (MOF) (HF: men> 6%, women > 7%; MOF: men> 15%, women> 12.5% which were based on the result of previous studies in Taiwan).

4.2 Exclusion Criteria

1. Unable to consent (e.g. dementia)
2. Have cancer under treatment
3. Have acute coronary syndrome (unstable angina, non-ST elevation myocardial infarction, ST-elevation myocardial infarction) or stroke in 3 months.
4. Limited cognitive or physical function for execute the intervention

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The elicitation of goals will be embedded into clinical programs routinely offered to patients with chronic kidney disease. Research coordinator will be trained to

complete the interviews.

The core components of interventions

- For participants with abnormal biochemical markers, pharmacological therapy and diet modification are applied.
- Dietary education on phosphorus additives is applied specifically for retention of phosphorus or high serum phosphorus level.
- Exercise for bone and cardiovascular health.
- Osteoporosis medications are initiated according to the reimbursed criteria of National Health Insurance, otherwise medications are used with non-insurance payment.

5.2 Handling of Study Interventions

Research coordinator

The Research coordinator will be a trained health professional (e.g. nurse, dietitian, case worker).

Responsibilities

1. Undergo training and preparation to elicit and document patients' interview.
2. Remind the participants to visit clinic on schedule.

Physicians

The clinician will be a licensed health care professional (MD).

Responsibilities

1. Know or review patient's disease and care preferences.
2. Review, discuss, and update patient's health priorities on each visit.
3.Prescribe medications for chronic kidney disease and osteoporosis according to the results of blood and urine examination, and bone density.

6 STUDY PROCEDURES

6.1 Schedule of Evaluation for Patient Population

Time period	Screening	Informed Consent (Enrollment)	Clinic visit	Interviews (Patient Reported Outcomes)	Blood and Urine Examination	Bone density and Thoracolumbar x-ray film
Enrollment (Day 1)	x	x	x		x	x
Follow-up Evaluation			x	x	x	

(3,6,9,12th month)						

6.2 Description of Research Assessments and Evaluations

6.2.1 Screening Evaluation

Potentially eligible patients will first be identified by administrative data within the Electronic Health Record (EHR). In the intervention arm, the primary care clinician will review the list and refer patients to a Research Coordinator at the practice who will be responsible for obtaining informed consent to participate in the trial. Interviews will be conducted primarily through the primary clinic. In the case that a potential participant does not meet the inclusion criteria or meet the exclusion criteria, they will be excluded. Participants in the trial will not receive payment.

6.2.2 Consent

Although this study involves minimal risk, every effort will be made to ensure that all potential participants understand the details of the study. Additionally, it will be made clear that refusing to participate will not affect eligibility to receive services or benefits. Potential participants will be asked to demonstrate their understanding of what participation involves. If it is unclear that participants demonstrate full understanding of what is being asked of them, staff will continue the discussion until consent has been fully clarified.

6.2.2 Assessments and Data Collection

For interviews, the result of questionnaire will be transcribed and transcripts will be coded by investigator of the research study. Qualitative interviews are analyzed using the constant comparative methodology. All coded material will be de-identified and aggregated for data analysis.

7 SAFETY ASSESSMENTS

It is the responsibility of the PI to oversee the safety of the study. Research data will be reviewed in a timely manner; communication with the IRB will be documented in an open and timely manner in accordance with existing policies; source documentation will exist for all data fields/questions; explanations for deviations from the study protocol will be recorded; and all study files and documents will be maintained in organized files. The IRB will also determine whether currently or previously enrolled participants should receive notice of the unanticipated problem (and the potential for possible risk).

7.1 Data Safety Monitoring Plan

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others, including adverse events, are not anticipated. In

the unlikely event that such events occur, Reportable Events [which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related] or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB.

8 RISKS AND BENEFITS

8.1 Risks

The risk of participants in this study may have a minor risk in blood sampling. Except for a slight pain in the skin at the blood draw, the chance of bleeding from the puncture site or microbial infection at the puncture site is very small.0000

8.2 Benefits

The potential benefit of the evaluation of this integrated approach will be to disseminate optimal care of CKD-MBD and osteoporosis. We expect that this approach will result in better care for the participants with CKD.

STATISTICAL CONSIDERATIONS

9.1 Sample Size

As this is a pilot study, we did not complete a formal sample size calculation. The chosen sample size is based upon the estimated number of patients that the funding supports their blood and urine examination, and bone density examination.

9.2 Outcomes

9.2.1 Primary outcomes

The primary outcome measures will be all-cause mortality, cardiovascular events, subsequent fracture rate, and fall rate from January 1, 2020 to December 31, 2020. The primary outcome measures will be collected during the baseline and follow-up (3-12 months) interviews in clinics.

9.4.2 Secondary outcomes

Secondary outcome measures will be biochemistry laboratory tests before and after multifaceted interventions.

9.4 Data Analyses

We will calculate descriptive statistics for participants' baseline characteristics and primary and secondary outcomes. The bivariate analysis will be performed using the t-test or Mann-Whitney U test for continuous variables with normal or non-

normal distribution, respectively. Chi-squared test for categorical variables will be used to test correlations between baseline characteristics, change of laboratory results and outcomes. The paired t-test will be used to examine the difference between before and after the interventions. Stepwise multivariate logistic regression models will be used to identify the correlates of outcomes after adjusting for potential confounders. All tests conducted will be two-tailed, and significance will be set at $p < 0.05$.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

A trained research coordinator and investigators will be responsible for entry of screening, enrollment, and medical records. Data inconsistencies and data abstraction errors will be dealt with initially by telephone or email with the research coordinator.

10.2 Data Management

Data coordination and management will occur within the National Taiwan University Hospital and its Chu-Tung Branch. Data management procedures will ensure accurate and efficient data collection and analysis; confidentiality, on-demand study monitoring reports. All data will be maintained for participant confidentiality and privacy. Access to data resources will be strictly limited to research coordinator and investigators, and the medical records and paper materials of this project are based on the principle of not leaving the hospital. The typed information will only be the research number of the respondent. All data is locked or placed on an encrypted computer, and only authorized personnel have permission to interpret it. The information collected by this project is only for the project team's medical research and academic publication.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent script and any subsequent modifications will be reviewed and approved by the Research Ethics committee of National Taiwan University Hospital responsible for oversight of the study.

11.2 Participant Confidentiality and Security

Information about study participants will be kept confidential. Any data, forms, reports, and other records will not leave the Hospital. All paper records will be kept in a locked file cabinet. For the qualitative interviews, at the completion of the coding and analysis the recordings and the link between study ID and identifying information will be destroyed, thus rendering the data anonymous.

12 RESULTS

12.1 Number of Patients Screened

A total of 249 patients in outpatient clinic of two investigators were screened for osteoporosis risk assessment. If FRAX® screening criteria for Hip fracture risk: men with risk > 6%, women > 7% or major fracture risk: men > 15%, Women > 12.5% were reached. Those with exclusion criteria were excluded. Finally, from January 1, 2020 to December 31, 2020, 5 participants were enrolled for multifaceted interventions. After the intervention, 5 people had laboratory testing, bone density examination and health education during follow-up but no one completed the study. The study was terminated because of funding was only for one year. A total of 133 patients were screened in National Taiwan University Hospital, and a total of 116 patients were screened in Chu-Tung Branch, with an average age of 75.7 years. A total of 138 patients accounted for 55.4% of men. The average weight of men was 66.3kg, the average women were 57.3kg, and the average serum creatinine level 2.0 mg/dL for men and 1.8 mg/dL for women. The estimated glomerular filtration rate (eGFR) was 41.9ml/min/1.73m^2 for men and 38.1ml/min/1.73m^2 for women (Table 1). In the analysis of the reasons for exclusion, the highest was the lower risk of fractures estimated by FRAX® which accounted for 128 (51.4%), followed by failure to perform behavioral interventions (17.7%) and patients' refusal (15.7%).

12.2 Baseline Status of Participants

Among the 5 participants, 2 were women and 3 were men. The average age is 85.2 years old, and the living situation is at most 40% living with foreign caregivers, indicating that this group may have higher care needs. For other comorbidities, all 5 participants had hypertension, 4 had type 2 diabetes mellitus, and 3 had osteoarthritis. All are common chronic diseases of the older adults. In the baseline biochemistry tests, the average value of creatine level was 1.6 mg/dL, iPTH level was 100.8 pg/mL, vitamin D level was 23.2 ng/mL, Alkaline phosphatase level was 65.3 U/L, and hsCRP was 0.17 mg/ dL, total cholesterol was 168.3 mg/dL low-density lipoprotein cholesterol was 109.3 mg/dL, high-density lipoprotein cholesterol was 40.3 mg/dL, blood calcium level was 2.3 mmol/L, blood phosphorus level was 3.5 mg/dL, average tubular reabsorption of phosphate was 79. Among the 5 participants, no one was diagnosed as chronic kidney disease-mineral bone disorder according to serum biochemistry examination, and cholesterol and inflammation marker were not elevated significantly.

12.3 Osteoporosis Related Variables

Among the osteoporosis-related variables, the average height was 157.8 cm, the

average weight was 62.9 kg, and the average body mass was 25.1. There were 4 participants with history of fractures before enrollment, 1 participant's parent with hip fractures, and all participants did not have other risk factors. The risk of major fracture (excluding BMD) was 17.2%, the risk of major fracture (including BMD) was 16.3%, the risk of hip fracture (excluding BMD) was 10.2%, and the risk of hip fracture (including BMD) was 9.4%. Only 1 participant was diagnosed with osteoporosis and received osteoporosis medication, 2 participants have exercise habits, and only 1 participant has the habit of supplementing calcium tablets and vitamin D.

12.4 Fall-related Assessment and Medical History

Before the enrollment, 2 participants had hip fracture, 2 participant had spine fracture, and 1 participant had ribs fracture. The residency before the fracture was 1 participant living with spouse, 1 participant living with children, 1 person in nursing home, and others living with foreign caregivers. These results showed a higher proportion of participants in needs of care. After the fractures, the mobility of 2 participants does not need assistive devices at all, and 3 participants need unilateral assistive devices to go out, which showed that hip fractures have a higher impact on walking ability.

12.5 Baseline Health Literacy

After explaining the impact of osteoporosis, behavioral intervention, medication use, and possible adverse reactions of medications, participant' understanding of health education content was less than 25% for 1 participant, 25-49% for 1 participant, and 50-74% for 2 participants, 75% or more is 1 participant. For information of medication use, the understanding level <25% was for 1 participant, 25-49% for 1 participant, 50-74% for 2 participants, more than 75% for 1 participant. Oral health education alone has limited effect on increasing the awareness of the disease in our participants.

Regarding the cause of chronic kidney disease and the signs of deterioration in renal function, what is glomerular filtration rate? What is urine protein? What are the choices of renal replacement therapies? Most participants do not understand. Only the impact of chronic kidney disease on your life, the goal of blood pressure control and the possible symptoms of chronic kidney disease would be the concern of participants, it showed that the participants have insufficient awareness of chronic kidney disease.

12.6 Changes during Tracking and outcomes

The 5 participants all completed the follow-up visits. However, they did not complete the full follow-up visits because the trial was terminated because the funding was only for one year. 4 participants met the conditions for the treatment of osteoporosis by the National Health Insurance, and all 4 were prescribed medications. 3 of them started treatment after osteoporosis was found in trial, and 1 of them interrupted the treatment and restarted during the trial. Drug treatment showed that this group needs more active screening and intervention for osteoporosis, so as to reduce the impact of osteoporosis on its health. During the follow-up period, no subjects experienced new fractures, new cardiovascular events, falls or deaths. There is no significant change statistically in the serum biochemistry examination.