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Concerted Action in Renal Osteosdystrophy (CAiRO)

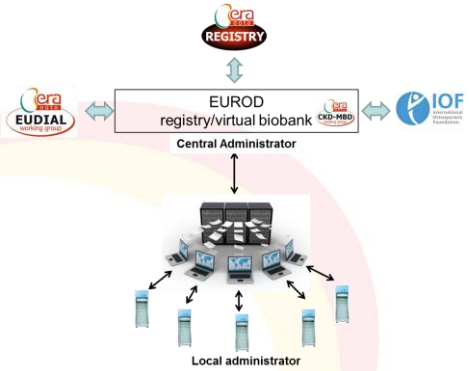
BACKGROUND: Renal osteodystrophy (ROD) is a complex disorder of bone metabolism that affects nearly all patients with CKD1-5. ROD is defined by the Kidney Disease Improving Global Outcomes (KDIGO) classification of bone Turnover, Mineralization and Volume (TMV). ROD may at least partly account for the high fracture burden in CKD. Clinical data correlating specific bone histomorphometry subtypes with fracture risks, however, are unavailable. ROD also has been linked to increased risk of vascular calcification and cardiovascular events. This association is commonly referred to as the bone vascular axis. The societal impact of both fractures and cardiovascular events as a consequence of (early) CKD, is probably severely underestimated, because despite the prevalence of CKD being high (over 10%), the preventive potential of early targeting ROD is overall neglected.

The primary goal of ROD treatment is reducing high bone turnover with calcitriol and its analogues and/or calcimimetics, at the same time as avoiding the development of low turnover through excessive use of these same agents. In addition, emerging data and clinical experience suggest that ROD with bone loss or fractures may be safely managed with treatments that are used for osteoporosis: anti-resorptives for high turnover ROD, and anabolics for low turnover ROD. Guidelines and clinical experience recommend that establishing the degree of turnover should be obtained prior to starting ROD treatment, and turnover should be monitored during the course of therapy because turnover may change, thus requiring treatment adjustments. Tetracycline double-labeled transiliac crest bone biopsy with histomorphometry is the gold standard method to define turnover; however, its widespread use in the clinic for either diagnosis or treatment monitoring is impractical. Therefore, the KDIGO best evidence guidelines recommend that clinical use of these agents is guided by the biomarkers parathyroid hormone (PTH) and bone specific alkaline phosphatase (BSAP). However, bone biopsy studies in CKD patients demonstrated that PTH and BSAP are poor guides for ROD treatment. Thus, there is an unmet clinical need to identify non-invasive biomarkers with better diagnostic accuracy than PTH and BSAP for the identification of turnover to guide ROD treatment decisions and for use in clinical trials.

MicroRNAs (miRNA) are small noncoding sequences of ~22 nucleotides that bind to the 3'-untranslated regions of mRNAs to silence gene expression by inhibiting translation or promoting degradation of target mRNAs. Recent studies indicate that miRNAs may act as important epigenetic regulators of function and differentiation of osteoblasts and osteoclasts during bone development and homeostasis(4). Meanwhile, also first promising data of miRNAs as biomarkers in bone disease have been published(5;6).

AIMS: The preset research project aims (1) to describe the epidemiology of ROD in Europe; (2) to evaluate whether the various ROD TMV classes confer different risks for incident fractures and cardiovascular morbidity and mortality, (3) to determine diagnostic test characteristics for discrimination of turnover-type by a priori defined bone-regulating circulating microRNAs, and (4) to initiate collaboration aimed at unraveling the contribution of bone to whole-organism physiology.

METHODS: This project consists of a population-based cohort study and a pilot biomarker study. It builds on unique epidemiological resources and cutting-edge analytical expertise, already available within the European-ROD (EUROD) initiative.



WP1: Epidemiology of ROD in Europe. In 2017, the EUROD initiative was launched under the umbrella of the ERA-EDTA CKD-MBD working group. Major aims of the initiative include the following: (1) to revitalize bone biopsy as a clinically useful tool in daily practice; (2) to promote and organize pan-European research in the field or ROD, (3) to improve and distribute knowledge in the field of ROD, and (4) to closely collaborate and interact with other bone and mineral societies across the world(7). As part of the initiative, a web-based bone biopsy registry has been built, complying with stringent European privacy rules. Relevant clinical, biochemical and histomorphometric parameters are collected in incident and prevalent bone biopsy cases. Availability of stored biomaterial (bone, vascular tissue, blood) is listed in a virtual biobank. At present, more than 350 bone biopsies, mostly from patients with end stage renal disease, have been enrolled. It is anticipated that by 2020, this number will increase to about 600. Undoubtedly, the EUROD registry and virtual biobank will prove to be a very useful repository for future epidemiological and clinical research.

WP2: ROD subtypes vs. hard bone and cardiovascular outcomes

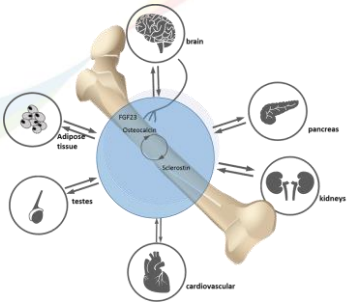
In close collaboration with local principal investigators/administrators, data on incident bone and cardiovascular endpoints as well as mortality will be collected in patients enrolled in the EUROD registry. The association between ROD subtypes and these endpoints will be investigated by cox regression analysis and (competing risk) survival analysis. Hazard ratios will be calculated for short-term (1 year) and longer-term (5 years) periods.

WP3: miRNAs discriminating bone turnover subtypes: a pilot study

Literature will be screened to identify bone-regulating miRNAs that may qualify as biomarker of bone turnover. In a subsequent pilot study including patients with histomorphometric proven low, normal and high bone turnover (n=20, each), the ability of these miRNAs (either alone or in panel) to discriminate high from nonhigh and low from nonlow turnover will be tested and compared to classical bone turnover markers. miRNAs will be measured by real time PCR analysis.

WP 4: Fostering interaction to better understand the contribution of bone to whole-organism physiology

Intense cross-talk exists between the skeleton and many other tissues and organs. The EUROD registry and biobanking available in participating centres may help to unravel relevant signaling pathways. In collaboration with other ERA-EDTA WGs and the International Osteoporosis Foundation (IOF), research questions will be listed that can be addressed by a concerted action.



GANTT CHART

We're convinced that this project can be successfully completed by one young fellow during a 1 year fellowship (Q1-Q4).

	Q1			Q2			Q3			Q4		
WP 1 Epidemiology of ROD in Europe.	M1	M2	M3	M1	M2	M3	M1	M2	M3	M1	M2	M3
Task 1.1. Harmonization and cross-validation of histomorphometric data												
Task 1.2. Data cleaning												
Task 1.3. Descriptive and correlation statistics												
Task 1.4. Report and dissimination												
WP 2 Relationship between ROD subtypes and hard bone and cardiovascular outcomes												
Task 2.1. collecting and coding data on hard outcomes												
Task 2.2. Statistical analysis												
Task 2.3. Report and dissimination												
WP 3 miRNAs discriminating bone turnover subtypes: a pilot study												
Task 3.1. Identification of candidate miRNAs												
Task 3.2. Construction of database												
Task 3.3. miRNA analyses												
Task 3.4. Statistical analysis												
Task 3.5. Report and dissimination												
WP 4 Fostering interaction												
Task 4.1. listing research questions EUROD-ERA-EDTA WGs												
Task 4.2. Listing research questions EUROD -International Osteoporosis Foundation												

DELIVERABLES: Present research project will inform on the epidemiology (prevalence, regional differences, temporal trends, and clinical and biochemical correlates) and implications of ROD in Europe. It will provide insights whether circulating bone-regulating miRNAs may outperform classical biomarkers (such as PTH and bone-specific alkaline phosphatase) as non-invasive biomarkers of ROD turnover-type. This information is of utmost relevance in an era in which personalized medicine becomes increasingly important. Finally, this research project will foster scientific cross-fertilization.

Reference List

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(2) Sprague SM, Bellorin-Font E, Jorgetti V, Carvalho AB, Malluche HH, Ferreira A, et al. Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis. Am J Kidney Dis 2016 Apr 1;67(4):559-66.

(3) Malluche HH, Porter DS, Monier-Faugere MC, Mawad H, Pienkowski D. Differences in bone quality in low- and high-turnover renal osteodystrophy. J Am Soc Nephrol 2012 Mar;23(3):525-32.

(4) Lian JB, Stein GS, van Wijnen AJ, Stein JL, Hassan MQ, Gaur T, et al. MicroRNA control of bone formation and homeostasis. Nat Rev Endocrinol 2012 Jan 31;8(4):212-27.

(5) Mandourah AY, Ranganath L, Barraclough R, Vinjamuri S, Hof RV, Hamill S, et al. Circulating microRNAs as potential diagnostic biomarkers for osteoporosis. Sci Rep 2018 May 30;8(1):8421.

(6) Feichtinger X, Muschitz C, Heimel P, Baierl A, Fahrleitner-Pammer A, Redl H, et al. Bone-related Circulating MicroRNAs miR-29b-3p, miR-550a-3p, and miR-324-3p and their Association to Bone Microstructure and Histomorphometry. Sci Rep 2018 Mar 20;8(1):4867.

(7) Evenepoel P, D'Haese P, Bacchetta J, Cannata-Andia J, Ferreira A, Haarhaus M, et al. Bone biopsy practice patterns across Europe: the European renal osteodystrophy initiative-a position paper. Nephrol Dial Transplant 2017 Mar 3.

DETAILS RELATED TO THE FELLOWSHIP

1. **Duration**: 12 months
2. **Location of the hosting centre**:

University Hospitals Leuven, Dialysis and Renal Transplantation unit
Herestraat 49, B-3000 Leuven, Belgium
Pieter.evenepoel@uzleuven.be and vera.voets@uzleuven.be

3. **Principal Investigator(s) of the project**:

Pieter Evenepoel, Prof.
Pieter.evenepoel@uzleuven.be, 003216344580

4. **Start of the fellowship**: January 2020.
5. **Essential requirements to be involved in the project**:
    MD with expertise in CKD-MBD (and focus on bone), preferentially postdoc
    Fluent in English
    Writing and organizational skills
    Knowledge of basic statistics (SAS,…)
    Knowledge of MS office (word-excel-access)
    Willing to travel across Europe (short stays)