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ERA Long-Term Research Fellowship Project

EUROD by CKD-MBD

Project's key info

Title of the project	**European collaborative effort to decrease fracture burden in CKD (EUFRAC)**
Working Group involved in the project	EUROD initiative by CKD-MBD Working Group
Principal Investigator(s) of the project	Pieter Evenepoel (Belgium)
Duration	12 months
Fellowship Grant	34.545,00 €
Start of the fellowship	Within 6 months after notification of the grant award to the fellow.

Receiving Institute

Name of receiving institute	University Hospitals Leuven, Dialysis and Renal Transplantation unit, Leuven, Belgium
Supervisor's name	Pieter Evenepoel (Belgium)
Supervisor's e-mail address	Pieter.Evenepoel@uzleuven.be

Project's detailed description

Project description

EUROD was launched in 2017 as an initiative of the ERA CKD-MBD Working Group. Major aims of the initiative include to revitalize bone biopsy as a clinically useful tool, to promote and organize pan-European research in the field of ROD, to improve and distribute knowledge in the field of ROD, and to closely collaborate and interact with other bone and mineral societies across the world. As part of the initiative, a web-based bone biopsy registry has been built, collecting relevant clinical, biochemical and histomorphometric parameters of bone biopsy cases, as well as detailing the availability of locally stored biomaterial (bone, vascular tissue, blood), thus functioning as a "virtual biobank". At present, the Registry contains more than 750 unique bone biopsy cases.

This project builds on the epidemiological resource of the EUROD Bone Biopsy Registry and the expertise available within the EUROD network.

The project will:

1) Inform on the landscape of ROD in Europe;
2) Develop a diagnostic tool for the non-invasive assessment of ROD;
3) Provide information on the clinical consequences of ROD and consist of the following work packages.

WP1: The EUROD Bone Biopsy Registry

In WP1, the fellow will assist in consolidating and expanding the EUROD Registry. Several centres are in the process of joining the registry or entering data, with the number of individual cases expected to increase to >1000 in the coming year. Further, the fellow will participate in ongoing quality assurance projects, including efforts to reach consensus on histomorphometric reference

values and diagnostic cutoffs of ROD and cross-validation of bone histomorphometric analyses performed at participating centres of EUROD. Finally, the fellow will initiate work to digitize the EUROD Registry as high-resolution images of bone biopsy slides and explore the utility of machine-learning statistical techniques and/or artificial intelligence for histomorphometric analysis.

WP2: Epidemiology of ROD in Europe

Since the turn of the millennium, low bone turnover seems to have replaced high bone turnover as the prominent disturbance of ROD, whereas overt osteomalacia is becoming increasingly rare. However, due to the dwindling number of bone biopsies performed, the current prevalence of different ROD phenotypes across stages of CKD is unknown. The EUROD Bone Biopsy Registry is well-suited to deliver such data. In WP2, the fellow will analyse this dataset to provide the first EUROD Registry based report on the prevalence of ROD phenotypes across stages of CKD; predialysis, on dialysis, and post-kidney transplantation.

WP3: The Digital Bone Biopsy

While the transiliac bone biopsy remains the gold standard to diagnose ROD, it cannot capture the dynamic changes of bone turnover, mineralization, and volume that occur in CKD, especially if bone-targeting treatment is introduced. In addition, it is an invasive procedure and rarely performed as part of routine clinical practice. Biochemical markers of skeletal remodelling show promise for the evaluation of bone turnover. Previously proposed diagnostic cut-offs demonstrate high negative predictive values, indicating clinical utility in ruling out both high and low bone turnover. Bone imaging can inform on bone mineral density and microstructure with relevance for clinical outcomes. The addition of demographic data and bone imaging, in combination with bone turnover and mineral metabolism markers, including changes in these parameters over time, may improve diagnostic precision and clinical relevance. Further, the currently proposed cut-offs for bone turnover markers have not been validated in external datasets. In WP3, the fellow will build on and extend previous efforts to provide an accurate, non-invasive assessment of ROD. The resulting algorithm will subsequently be validated in external datasets. WP3 aims to deliver an app-based or online tool for clinical use, which should provide an estimate of the ROD phenotype based on demographic, imaging, and biochemical data.

WP4: Clinical consequences of ROD

The clinical consequences of ROD remain uncertain which likely contributes to the widespread nihilism in the treatment of CKD-associated osteoporosis. Further, this knowledge gap represents a major barrier for the establishment of well-defined treatment targets. The EUROD Registry gathers prospective data on incident bone and cardiovascular endpoints as well as mortality. In this WP, the association between ROD subtypes and patient-relevant outcomes will be explored. Collaboration with the ERA Registry will be sought, to secure validated patient-relevant outcomes. Further, advanced statistical methods will be applied to explore whether certain patterns of bone histomorphometric parameters carry prognostic information.

Goals of the project

Goals of this project include:

1) Consolidation and expansion of the EUROD Bone Biopsy Registry;
2) Publication of the first report of data from the EUROD Bone Biopsy;
3) Registry on the landscape of ROD across stages of CKD in Europe;
4) Development of a non-invasive diagnostic tool for the assessment of ROD, ready for clinical application;
5) Delivering information on the clinical consequences of different ROD phenotypes.

Qualifications and/or expertise required to the fellow

Applicants should be early career academics (PhD or post-doctoral level) and must have:

- Research experience within the field of CKD-MBD, or clinicians (senior trainees, junior staff) with a strong interest in CKD-MBD;
- Statistical expertise, particularly within the field of machine learning or artificial intelligence will be recognized as an advantage.