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Full Review

Bone biopsy practice patterns across Europe: the European renal osteodystrophy initiative—a position paper

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ABSTRACT

Renal osteodystrophy (ROD) is a heterogeneous group of metabolic bone diseases complicating progressive chronic kidney disease (CKD). Bone biomarkers and bone imaging techniques may help to assess bone health and predict fractures in CKD but do have important inherent limitations. By informing on bone turnover and mineralization, a bone biopsy may help to guide prevention and treatment of ROD and its consequences. According to a recent survey conducted among European nephrologists, bone biopsies are performed rather exceptionally, both for clinical and research purposes. Obviously, clinical research in the field of ROD is threatened by vanishing clinical and pathological expertise, small patient cohorts and scientific isolation. In March 2016, the European Renal Osteodystrophy (EU-ROD) initiative was created under the umbrella of the ERA-EDTA CKD-mineral and bone disorder (MBD) Working Group to revitalize bone biopsy as a clinically useful tool in the diagnostic workup of CKD-MBD and to foster research on the epidemiology, implications and reversibility of ROD. As such, the EU-ROD initiative aims to increase the understanding of ROD and ultimately to improve outcomes in CKD patients.

Keywords: biomarkers, bone mineral density, chronic renal failure, hyperparathyroidism, renal osteodystrophy

INTRODUCTION

Renal osteodystrophy (ROD) is a heterogeneous group of metabolic bone diseases that accompanies progressive chronic kidney disease (CKD). These metabolic bone diseases have specifically defined quantitative histomorphometric diagnostic criteria as well as clinical features [1]. More recently, the Kidney Disease: Improving Global Outcomes (KDIGO) Working Group offered a new and more encompassing definition of renal bone disease, i.e. CKD-mineral and bone disorder (MBD)

[2]. This more general definition recognizes that the pathophysiology of renal bone disease extends beyond the skeleton and that there are links between abnormal bone remodelling activity and the risk for soft tissue and vascular calcification (commonly referred to as the bone–vascular axis). In this new construct, the term ROD is limited to the specific changes in bone histology seen in CKD. Besides playing a crucial role in locomotion, the skeleton is increasingly recognized as an endocrine organ capable of producing various hormones involved in energy, glucose and mineral metabolism [3]. Thus the bone may be not only a target but also a driver of mineral disturbances in CKD.

Clinical research in the field of ROD lags behind and is threatened by vanishing clinical and pathological expertise in bone biopsy retrieval and reading, small patient cohorts and scientific isolation. ROD, however, is not innocent, as it may result in fractures, bone pain, deformities in growing children, reduced growth velocity/peak bone mass and abnormal height and indirectly to vascular calcification and increased (cardiovascular) mortality [1, 4]. Bone biomarkers [5] and bone imaging techniques [dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), high-resolution peripheral quantitative computed tomography (HR-pQCT), 18F-fluoride positron emission tomography, etc.) may help to assess bone health and predict fractures in CKD, but do have important inherent limitations. A bone biopsy, performed after tetracycline labelling, allows definitive assessment of the material and structural characteristics that contribute to bone quality and hence to bone strength [6]. Several complementary analytical techniques can be applied, including microscopy (histomorphometry and immunohistochemistry), imaging techniques, spectrometry and molecular diagnostics [7]. In daily clinical practice, a bone biopsy may greatly facilitate clinical decision making by informing on bone turnover and mineralization.

Patients with CKD are at increased risk of fractures. The fracture risk steadily increases along the progression of renal disease to become four times higher in end-stage renal disease patients than in non-renal counterparts [8]. The risk further increases, at least transiently, following renal transplantation [9]. Compared with those without fractures, patients with CKD experience a multifold increased risk of mortality [10].

Both a high fall risk [11] and impaired bone strength account for the increased fracture risk in CKD. Bone strength is determined by bone quantity and bone quality. Several lines of evidence indicate that CKD is a state of low bone mass and accelerated bone loss [12]. Bone mass can be evaluated non-invasively by imaging techniques such as DXA and pQCT. It is increasingly acknowledged that, similar to the general population, low bone mineral density (BMD) predicts fracture risk in CKD. Since adjustment for bone mineral density (BMD) does not nullify the association between CKD and increased fracture risk, CKD may be equally considered a state of impaired bone quality. Bone turnover, mineralization, microarchitecture, microfractures and matrix and mineral composition are all important determinants of bone quality. A bone biopsy remains at present a prerequisite for proper evaluation of bone quality. Non-invasive analytical approaches such as biomarkers and isotope and imaging techniques are available, but their clinical utility in CKD is still being assessed. It is unlikely, however, that these techniques will render bone biopsies obsolete in the workup of low-impact fractures or unexplained bone pain in the setting of advanced CKD (with or without a functioning transplant). These techniques will complement rather than replace bone biopsy as a diagnostic tool.

Here we present the results of a pan-European survey on the use of bone biopsies in the management of ROD. We also propose the formation of a European network to facilitate research and improve the management of ROD.

BONE BIOPSY PRACTICE PATTERN: A EUROPEAN SURVEY

Despite being considered the gold standard in diagnosing renal bone disease, bone biopsies are performed rather exceptionally in daily clinical practice. To get a better insight into current bone biopsy practice patterns and attitudes towards the procedure across Europe, an electronic survey was sent out in May 2015 to all European members of the ERA-EDTA CKD-MBD Working Group ($n = 230$), complemented by European opinion leaders ($n = 13$). Seventy-eight invitees completed the survey, corresponding to a response rate of 32%. All regions of Europe were represented. The main activity of the respondents was clinical nephrology (50%), followed by dialysis (26%), transplantation (9%) and research (9%). The majority of respondents (89%) work in tertiary academic referral hospitals. The following paragraphs summarize the main results of the survey.

Current practice patterns. Half of the respondents reported having performed bone biopsies in the past 5 years; among them, 27.2% performed bone biopsies for research purposes only. Most respondents thus perform bone biopsies for clinical purposes. The total number of bone biopsy procedures per respondent over the last 5 years was low, being <10. In 58.9% of the cases, nephrologists were in charge of the bone biopsy procedure. In other centres, bone biopsies were performed by surgeons (12.5%) or rheumatologists (5.4%). The (trans)iliac horizontal approach was most commonly used (65.5%), followed by the vertical approach (29.1%). Only a few (8.0%) performed drill-assisted bone biopsies. Small (inner diameter <5 mm) and non-disposable trephine needles are gaining in popularity (almost 40% penetrance) at the expense of the large, non-disposable Bordier and Bedford trephine needles. Most procedures (66.7%) were performed with local anaesthesia in combination with light sedation (midazolam). Histomorphometry was mostly performed in external laboratories.

Indications. Most respondents agreed on the following bone biopsy indications: low-impact fracture, unexplained bone pain, prior to parathyroidectomy (to confirm high bone turnover) or initiation of antiresorptive drugs (to exclude low bone turnover), unexplained hypercalcaemia or radiologic abnormality and suspected or proven overload or toxicity to heavy or rare metals. Also, a discordance between parathyroid hormone (PTH) and alkaline phosphatase levels is considered an indication for a bone biopsy by almost 50% of the respondents. Most respondents consider a stand-alone PTH level outside the

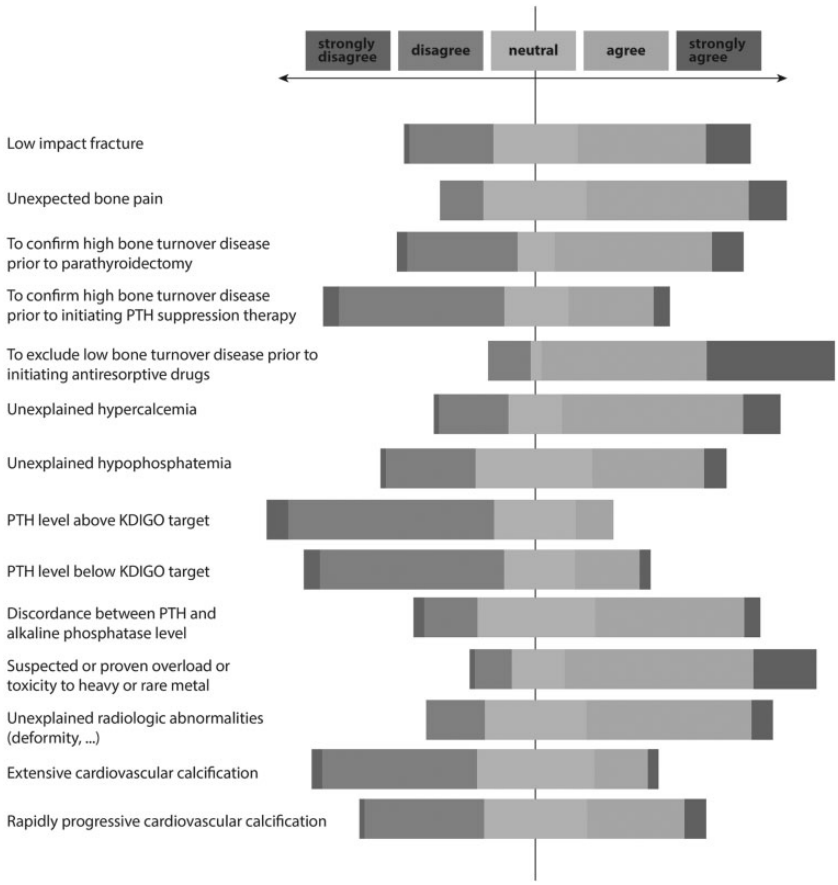

FIGURE 1: Responses to statement: 'Please indicate whether you agree or not following potential indications to perform a bone biopsy.' Percentage distribution.

KDIGO target range insufficient to proceed with a bone biopsy. While a majority of respondents consider a bone biopsy valuable to confirm high bone turnover before parathyroidectomy, they mostly disagree with the statement that it should be performed before initiating PTH suppressive therapy (calcimimetics, active vitamin D analogues) (Figure 1).

Limitations/hurdles. Multiple hurdles hampering the widespread implementation of bone biopsies were identified. These included a laborious sampling procedure, time-consuming and costly histopathological analysis and missing histopathological expertise. Of the respondents, 51% state that procedural pain is a hurdle to the widespread implementation of bone biopsy as a diagnostic clinical tool (Figure 2). Of interest, most respondents disagree with the statement that a bone biopsy is mainly a research tool with little clinical added value.

In aggregate, the results of this survey teach us that a bone biopsy overall is perceived as an invasive, painful, laborious but clinically useful procedure and that histomorphometric expertise is not widely available. Histomorphometry, moreover, is complex, time-consuming and costly, all important hurdles in an era in which cost savings and immediate feedback are increasingly appreciated. Consequently, bone biopsies at present are nowhere part of routine assessment and follow-up and are performed in specific cases in a limited number of centres only. A negative spiral is ongoing, which may finally result in complete disappearance of the expertise.

THE EU-ROD INITIATIVE

In an attempt to halt this negative spiral the European Renal Osteodystrophy (EU-ROD) initiative was created under the umbrella of the ERA-EDTA CKD-MBD Working Group. EU-ROD's primary mission is to revitalize bone biopsy as a clinically useful tool in the diagnostic workup of CKD-MBD and to facilitate research on the epidemiology, implications and reversibility of ROD.

A bone biopsy is deemed an interesting scientific tool [13], but only seldom is it considered in daily clinical practice. The perception of the clinical usefulness of a bone biopsy is often negative, as less invasive and demanding approaches have become available. In particular, the reduced procedural complexity and morbidity related to the use of smaller and disposable trephine needles may lower the threshold for performing a bone biopsy. There is almost no trade-off, as most procedures with these needles yield sufficient bone tissue for bone histomorphometry. Even more threatening for the survival of bone biopsy as a diagnostic procedure is the vanishing reservoir of experts in clinical histomorphometry. Both a low clinical demand and budgetary restrictions erased interest in bone histomorphometry for clinical purposes.

Today, epidemiological studies investigating the pattern of ROD across stages of CKD and its evolution over the years are

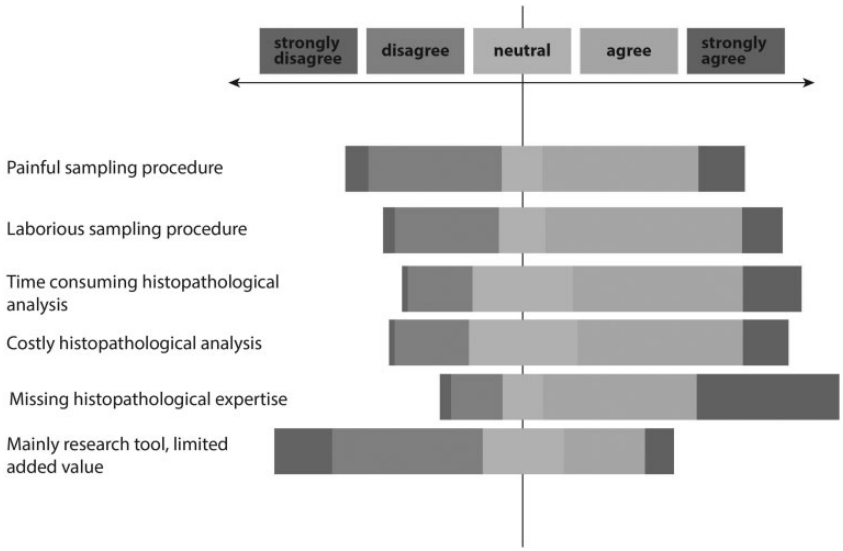

FIGURE 2: Responses to question: 'What are in your opinion hurdles to a more widespread clinical implementation of bone biopsies in CKD patients?' Percentage distribution.

sparse and often flawed by selection bias. Published data may not be valid, given that a considerable proportion of biopsies were retrieved during research projects. Also, regional differences in ethnic background, demographics and CKD-MBD treatment may limit the applicability of global collaborative reports for local health care practitioners. A European collaboration of clinicians, specializing in treating bone disorders in CKD and in retrieving bone biopsies in clinical settings, could result in more valid epidemiological data.

Studies investigating the association between indices of bone quality and prevalent and incident fractures are limited, if not non-existent. An overarching cohort study combining bone biopsy databases from different European centres would offer a blueprint of contemporaneous renal bone disease in Europe and may be hypothesized to offer hints to biological factors and mechanisms underlying the increased fracture risk in CKD.

The armamentarium to tackle age-related osteoporosis is rapidly expanding [14]. Clinical trials of senile osteoporosis therapy generally exclude patients with advanced kidney disease. The lack of information with regards to the role, efficacy and safety of established and novel agents for the treatment of osteoporosis in these patients paves the way for therapeutic nihilism. *Post hoc* analyses of large studies in post-menopausal women showed a similar benefit in CKD patients as in the general population. However, those CKD patients did not have biochemical abnormalities associated with CKD-MBD. Additional studies are urgently required to evaluate the efficacy and safety of antiresorptive and anabolic agents in the setting of CKD. A European collaborative effort offers the best soil for initiating and successfully completing such intervention studies.

After kidney transplantation, bone disorders often persist due to incomplete recovery of pre-existing disturbances of mineral metabolism, *de novo* CKD-MBD due to reduced kidney graft function and the negative effect of immunosuppression on bone [15]. However, little is known about the association of laboratory abnormalities with bone disorders, vascular pathology and outcome after kidney transplantation. The few and small bone biopsy studies that have been performed suggest a poor association of circulating bone turnover markers and bone histomorphometric findings and an increasing prevalence of low bone turnover with time from transplantation [16–19]. The EU-ROD initiative will facilitate further exploration of the pathophysiology of post-transplant CKD-MBD and enable the performance of interventional studies aimed at treatment and prevention of bone and vascular complications.

The aims of the EU-ROD initiative include the following:

1. To revitalize bone biopsy as a clinically useful tool in daily practice. Bone biopsies should regain a prominent place in daily practice to help tailor CKD-MBD therapy for individual patients, a relevant goal in an era favouring personalized medicine. We envisage the following initiatives to achieve this aim:
   a. Organize hands-on workshops and training programs for clinicians and pathologists to spread expertise in the field.
   b. Harmonize the bone biopsy procedure, sample handling and reading [standard operating procedures (SOPs)]. Publish SOPs with regard to the bone biopsy procedure, analysis and reporting.
   c. Harmonize units of the various histomorphometric parameters among histopathology labs to facilitate comparison and interpretation of results.
   d. Define normal ranges for static and dynamic histomorphometric parameters.
   e. Report on the pattern of ROD in contemporaneous European CKD patients.
2. To promote and organize pan-European research in the field of ROD. We foresee the following initiatives to achieve this aim:
   a. Create an online repository of existing European clinical material and a network of investigators in the field of ROD.

b. Identify research questions that can be addressed by pooling existing data once the repository is created. These questions may relate to the epidemiology, implications and reversibility/treatment of ROD.
c. Develop SOPs for diagnosis, including the bone biopsy procedure, analysis and reporting, (see above), circulating bone biomarkers and imaging techniques.
d. Although bone biopsy is considered the gold standard for evaluating bone health, there is at present no proof that bone histomorphometry outperforms clinical, biochemical and radiological indices as a hard outcome risk predictor. The present initiative will address the question whether more frequent bone biopsies result in a decreased fracture burden (and related morbidity and mortality).
e. Search for a less demanding but equally relevant and accurate analytical alternative to classical histomorphometry for the diagnosis of ROD. Classical operator-dependent histomorphometry is very laborious and time consuming, curtailing 'routine' analysis. Circulating bone-specific biomarkers [20], as well as isotope [21] and imaging techniques (MRI, HR-pQCT, 18F-fluoride positron emission tomography, etc.), though promising non-invasive alternatives to bone biopsy, so far do not provide information as precise as that provided by bone histomorphometry in CKD. Currently available bone biomarkers fail in distinguishing low from normal bone turnover. Additional validation studies in larger cohorts with simultaneous bone histomorphometry data across the whole spectrum of CKD-MBD are mandatory.
f. To initiate and support clinical intervention studies aimed at ameliorating ROD and fracture risk.
g. To facilitate fund raising for research at national and European levels.

3. To improve and distribute knowledge in the field of ROD. We envisage the following initiatives to achieve this aim:
   a. Collaborate with the European Best Practice Guideline group in the updating process of guidelines related to the care of ROD patients.
   b. Collaborate with the ERA-EDTA Registry and European Dialysis Outcomes and Practice Patterns Study initiative to evaluate current practice patterns with regard to the evaluation of ROD.
   c. To collaborate on educational activities regarding ROD within the ERA-EDTA (CKD-MBD Working Group), including (i) organization of an annual working group meeting, (ii) the preparation of position papers and review articles on relevant ROD issues and (iii) the organization of symposia (including workshops) specifically dedicated to ROD and by extension CKD-MBD.
4. To closely collaborate and interact with similar initiatives elsewhere in the world, e.g. the Brazilian Registry of Bone Biopsy (Registro Brasileiro de Biópsias Ósseas) [22].
5. To closely collaborate with other bone and mineral societies around the world.

CONCLUSION

It is time to halt the negative spiral of bone biopsy procedures. Bone histomorphometry often remains indispensable in the workup of low-impact fracture in the setting of advanced CKD, which is a common complication among CKD patients. The prevention and treatment of low-impact fractures in CKD patients is challenging and at the same time it is frustrating because of a lack of evidence. More widespread implementation of bone biopsies as a diagnostic procedure may widen the therapeutic horizon and foster the development and validation of more reliable, non-invasive diagnostic tools.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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