
Article:
Evenepoel, P., D'Haese, P., Bacchetta, J. et al. (2017) Bone biopsy practice patterns across Europe: the European renal osteodystrophy initiative - a position paper. Nephrology Dialysis Transplantation, 32 (10). pp. 1608-1613. ISSN: 0931-0509

https://doi.org/10.1093/ndt/gfw468

The EUropean Renal OsteoDystrophy (EUROD) initiative: time to revitalize bone biopsy as a diagnostic tool in daily clinical care and research in CKD

A position paper

Evenepoel P[1], D'Haese P[2], Bachetta J, Cannata-Andia J, Ferreira A, Haarhaus M[6], Mazzofero, S, Lafage Proust MH, Salam S[9], Spasovski G, Cozzolino M

1. KU Leuven – University of Leuven, Department of Immunology and Microbiology, Laboratory of Nephrology and University Hospitals Leuven, Department of Nephrology and Renal Transplantation, B-3000 Leuven, Belgium

2. Antwerp University, Department of Biomedical Sciences, Laboratory of Pathophysiology, B-2610 Wilrijk, Belgium

…. 9. Sheffield Kidney Institute and Academic Unit of Bone Metabolism, Sheffield Teaching Hospitals NHS Foundation Trust, S5 7AU Sheffield, United Kingdom.

…..

6. Karolinska Institutet, Department of Clinical Science, Intervention and Technology, Division of Renal Medicine and Karolinska University Hospital, Department of Nephrology, SE-17176 Stockholm, Sweden

Abbreviated Title: EUROD initiative

Key terms: Bone

***Word count manuscript*:** 2229 (max 3000)

Word count abstract: 245 (max 250)

***Number of figures and tables*:** 2

Address for correspondence: P. Evenepoel, MD, PhD
Nephrology
University Hospitals Leuven
Herestraat 49
B-3000 Leuven

BELGIUM

Tel. +32-16-344591

Fax. +32-16-344599

e-mail: Pieter.Evenepoel@uzleuven.be

[1]The authors declare no funding or conflicts of interest.

ABSTRACT

Renal osteodystrophy (ROD) is a heterogeneous group of metabolic bone diseases that accompanies 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. A bone biopsy, performed after tetracycline labeling allows the proper assessment of the material and structural characteristics that contribute to bone quality and hence to bone strength. As confirmed by a recent survey among European nephrologists, bone biopsies are performed rather exceptionally, both for clinical and research purposes. Clinical research in the field of ROD is threatened by vanishing clinical and pathological expertise, small patient cohorts, and scientific isolation. The EUropean Renal OsteoDystrophy (EUROD) initiative was recently created under the umbrella of the ERA-EDTA CKD-MBD working group to revitalize bone biopsy as a clinical useful tool in the diagnostic workup of CKD-MBD and to foster research on the epidemiology, implications and reversibility of ROD. As such, the EUROD initiative aims to increase the understanding of ROD and ultimately to improve outcomes in CKD patients.

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 working group offered a new and more encompassing definition of renal bone disease, i.e. CKD-mineral and

bone disorder (CKD-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 remodeling 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]. The bone thus may not only be 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, and abnormal height and indirectly to vascular calcification and increased (cardiovascular) mortality[1;4]. Bone biomarkers[5] and bone imaging techniques (DXA, MRI, hr-pQCT, 18F-fluoride positron emission tomography …) may help to assess bone health and predict fractures in CKD, but do have important inherent limitations. A bone biopsy, performed after tetracycline labeling allows the proper assessment of the material and structural characteristics that contribute to bone quality and hence to bone strength[6].

Patients with CKD are at increased risk of fractures. The fracture risk steadily increases along the progression of renal disease to become 4 times higher in end stage renal disease patients than in non-renal counterparts[7]. The risk further increases, at least transiently, following renal transplantation[8]. Compared with those without fractures, patients with CKD experience a multifold increased risk of mortality[9].

The challenge for physicians managing fragility fractures in patients with CKD is discriminating fractures due to senile osteoporosis from fractures due to ROD[10]. Both a high fall risk[11]and an 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 BMD predicts

fracture risk in CKD. Since adjustment for 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 developed. It is however unlikely that these techniques will render bone biopsies obsolete in the work-up of low impact fractures or unexplained bone pain in the setting of advanced CKD. 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 or ROD. We also propose the formation of a European network to facilitate research and improve 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 in 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 to have performed bone biopsies in the past 5 years; among them, 27.2% have performed bone biopsies for research purposes only. Most respondents thus perform bone biopsies for clinical purposes. The total number of procedures per respondent over the last 5 years was low, being less than 10. In 58.9 % of the cases, nephrologists were in charge of the bone biopsy procedure. In other

centers, 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 few (8.0%) performed drill-assisted bone biopsies. Small (inner diameter < 5mm) and non-disposable trephine needles are gaining 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 hypercalcemia or radiologic abnormality, and suspected or proven overload or toxicity to heavy or rare metal. Also, a discordance between PTH and alkaline phosphatase level is considered an indication for a bone biopsy by almost 50% of the respondents. Most respondents consider a stand-alone PTH level outside the KDIGO target range insufficient to proceed with a bone biopsy. While a majority of respondents consider a PTX valuable to confirm high bone turnover before parathyroidectomy, they mostly disagree with the statement that a bone biopsy should be performed before initiating PTH suppressive therapy (calcimimetics, active vitamin D analogs) (figure 1).

Limitations/hurdles: Multiple hurdles hampering the widespread implementation of bone biopsies were identified. These included laborious sampling procedure, time consuming and costly histopathological analysis, and missing histopathological expertise. Fifty-one percent of the respondents state that procedural pain is a hurdle to the widespread implementation of bone biopsy as a diagnostic clinical tool (figure 2).

In aggregate, the results of this survey teach us that a bone biopsy overall is perceived as an invasive, painful, laborious 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 centers

only. A negative spiral is ongoing, which finally risks to result in the complete disappearance of the expertise.

THE EUROD INITIATIVE

In an attempt to halt this negative spiral the EUropean Renal OsteoDystrophy (EUROD) initiative was created under the umbrella of the ERA-EDTA CKD-MBD working group. EUROD's primary mission is to revitalize bone biopsy as a clinical 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 considered in daily clinical practice. A bone biopsy has a negative connotation, which may be dated as less invasive and demanding approaches have become available. Especially 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 tradeoff 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 step by step interest in clinical histomorphometry.

Today, epidemiological studies on the pattern of ROD across stages of CKD are 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, specialized on treating bone disorders in CKD and on retrieving bone biopsies in clinical settings, could result in more valid epidemiologic data and serve as a forum for interventional studies involving bone biopsies.

Studies investigating the association between indices of bone quality and prevalent and incident fractures are limited. An overarching cohort study, combing bone biopsy databases from different European centers, would offer a blueprint of contemporaneous renal bone disease in Europe and may offer hints to biological factors and mechanisms underlying the increased fracture risk in CKD.

The armamentarium to tackle senile osteoporosis is rapidly expanding[10]. Clinical trials of senile osteoporosis therapy generally excluded patients with advanced kidney disease. This leaves nephrologists with ignorance with regard to role, efficacy and safety of established and novel agents for the treatment of osteoporosis in these patients ~~and~~ paves the way for therapeutic nihilism. Post-hoc analyses of large studies in postmenopausal women showed a similar benefit in CKD patients without biochemical abnormalities suggesting CKD-MBD as in the general population. Additional studies are urgently required to evaluate the impact of antiresorptive and anabolic agents on bone health and fracture risk in CKD patients. 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[14]. 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 dissociation of circulating bone turnover markers and bone histomorphometric findings and an increasing prevalence of low bone turnover with time from transplantation [15-18]. The EUROD 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 EUROD 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 tailoring CKD-MBD therapy for the individual patient, a relevant goal in era favoring personalized medicine. We envisage the following initiatives to achieve this aim:
    a. Organize hands on workshops for clinicians and pathologists spreading expertise in the field
    b. Harmonize the bone biopsy procedure, sample handling and reading (standard operating procedures, SOP). Publish SOP, both with regard to the bone biopsy procedure, analysis and report.

c. Define normal ranges for static and dynamic histomorphometric parameters
d. Report on the pattern of ROD in contemporaneous European CKD patients

2. To promote and organize pan-European research in the field or ROD. We foresee the following initiatives to achieve this aim:
    a. Create an online repository of existing European clinical material and network of investigators in the field of renal osteodystrophy
    b. Identify research networks and 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 standard operating procedures (SOP) for diagnosis, including the bone biopsy procedure, analysis and report (see above), bone biomarkers and imaging techniques.
    d. Search for a less demanding but equally relevant and accurate analytical alternative to classical histomorphometry for the diagnosis of ROD. Classical 'operator depending' histomorphometry is very laborious and time-consuming, curtailing 'routine' analysis. Bone biomarkers [19], isotope [20] and imaging (MRI, HR-pQCT, 18F-fluoride positron emission tomography…) techniques, though promising non-invasive alternatives for bone biopsy, so far did not fulfill expectations in CKD. Additional validation studies in larger cohorts with simultaneous data on bone histomorphometry across the spectrum of CKD are mandatory.
    e. To initiate and support clinical intervention studies aimed at ameliorating ROD and fracture risk
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.
    b. Collaborate with ERA-EDTA registry and EURODOPPS initiative to evaluate current practice patterns with regard to evaluation of ROD.
    c. To collaborate on educational activities around ROD within the ERA-EDTA (CKD-MBD working group) including a) the organization of an annual working group meeting; b) preparation of position papers and review articles on

relevant ROD issues; c)the organization of symposia (including work-shops) specifically dedicated to ROD.

4. To closely collaborate and interact with similar initiatives elsewhere in the world, e.g. REBRABO[21].
5. To closely collaborate with other bone and mineral societies across the world

CONCLUSION

It is time to halt the negative spiral of bone biopsy procedures. A bone biopsy often remains indispensable in the work-up of low-impact fracture in the setting of advanced CKD. Low-impact fractures are common among CKD patients. Their prevention and treatment is challenging and at the same time frustrating, because the lack of evidence. A more widespread implementation of bone biopsies as diagnostic procedure may widen the therapeutic horizon and may foster the development and validation of non-invasive alternatives.

ACKNOWLEDGMENTS

The authors want to thank all those who completed the survey. The authors also thank the member of the ERA-EDTA CKD-MBD working group for supporting the initiative and for providing constructive comments.

FIGURE LEGENDS

Figure 1.: Responses to question: “Please indicate whether you agree or not following potential indications to perform a bone biopsy”. Percentage distribution: grey: neutral; light green: agree; dark green: strongly agree; orange: disagree; red: strongly disagree.

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: grey: neutral; light green: agree; dark green: strongly agree; orange: disagree; red: strongly disagree.

Figure 1:

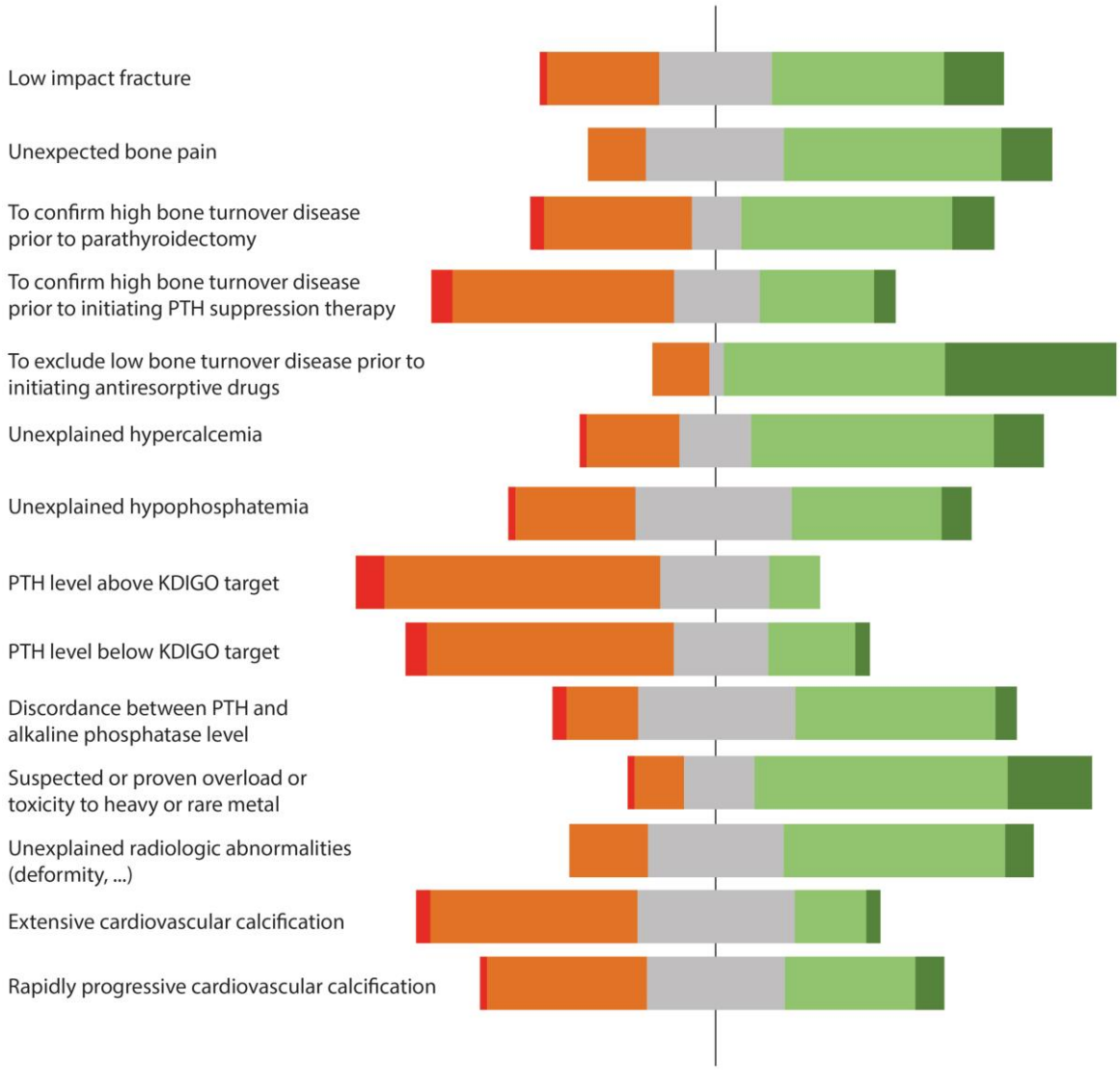
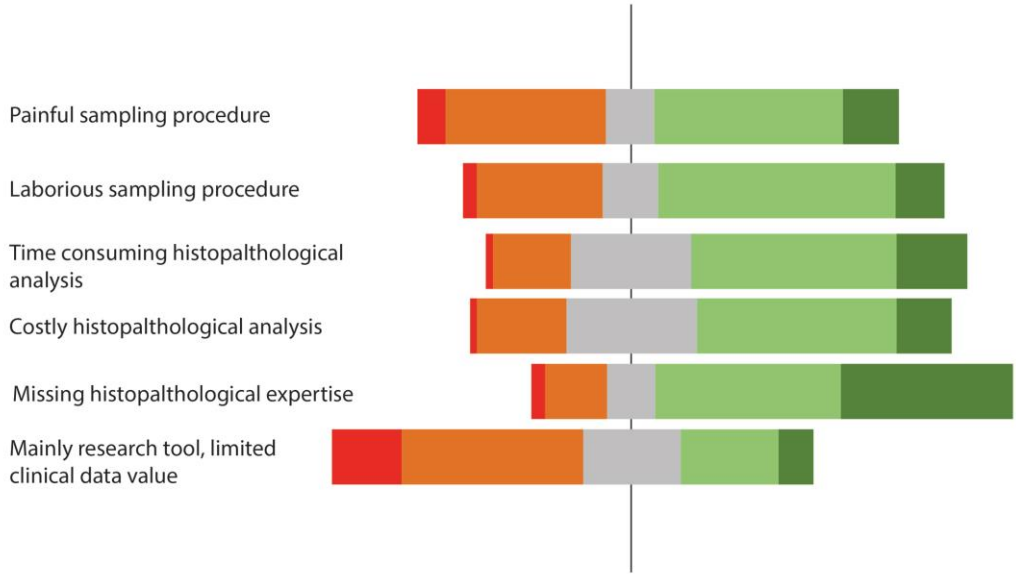

Low impact fracture
Unexpected bone pain
To confirm high bone turnover disease prior to parathyroidectomy
To confirm high bone turnover disease prior to initiating PTH suppression therapy
To exclude low bone turnover disease prior to initiating antiresorptive drugs
Unexplained hypercalcemia
Unexplained hypophosphatemia
PTH level above KDIGO target
PTH level below KDIGO target
Discordance between PTH and alkaline phosphatase level
Suspected or proven overload or toxicity to heavy or rare metal
Unexplained radiologic abnormalities (deformity, ...)
Extensive cardiovascular calcification
Rapidly progressive cardiovascular calcification

Figure 2


Painful sampling procedure
Laborious sampling procedure
Time consuming histopalthological analysis
Costly histopalthological analysis
Missing histopalthological expertise
Mainly research tool, limited clinical data value

Reference List

(1) Ott SM. Bone histomorphometry in renal osteodystrophy. *Semin Nephrol* 2009;29:122-132.

(2) Moe S, Drueke T, Cunningham J et al. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *kidney int* 2006;69:1945-1953.

(3) Vervloet MG, Massy ZA, Brandenburg VM et al. Bone: a new endocrine organ at the heart of chronic kidney disease and mineral and bone disorders. *Lancet Diabetes Endocrinol* 2014;2:427-436.

(4) Salam SN, Eastell R, Khwaja A. Fragility fractures and osteoporosis in CKD: pathophysiology and diagnostic methods. *Am J Kidney Dis* 2014;63:1049-1059.

(5) Cavalier E, Delanaye P, Moranne O. Variability of new bone mineral metabolism markers in patients treated with maintenance hemodialysis: implications for clinical decision making. *Am J Kidney Dis* 2013;61:847-848.

(6) Torres PU, Bover J, Mazzaferro S, de Vernejoul MC, Cohen-Solal M. When, how, and why a bone biopsy should be performed in patients with chronic kidney disease. *Semin Nephrol* 2014;34:612-625.

(7) Jadoul M, Albert JM, Akiba T et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *kidney int* 2006;70:1358-1366.

(8) Ball AM, Gillen DL, Sherrard D et al. Risk of Hip Fracture Among Dialysis and Renal Transplant Recipients. *JAMA* 2002;288:3014-3018.

(9) Tentori F, McCullough K, Kilpatrick RD et al. High rates of death and hospitalization follow bone fracture among hemodialysis patients. *Kidney Int* 2014;85:166-173.

(10) Miller PD. Bone disease in CKD: a focus on osteoporosis diagnosis and management. *Am J Kidney Dis* 2014;64:290-304.

(11) Naylor KL, McArthur E, Leslie WD et al. The three-year incidence of fracture in chronic kidney disease. *Kidney Int* 2014;86:810-818.

(12) Nickolas TL, Stein EM, Dworakowski E et al. Rapid cortical bone loss in patients with chronic kidney disease. *J Bone Miner Res* 2013;28:1811-1820.

(13) Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009;113:S1-S130.

(14) Evenepoel P. Recovery versus persistence of disordered mineral metabolism in kidney transplant recipients. *Semin Nephrol* 2013;33:191-203.

(15) Rojas E, Carlini RG, Clesca P et al. The pathogenesis of osteodystrophy after renal transplantation as detected by early alterations in bone remodeling. *kidney int* 2003;63:1915-1923.

(16) Borchhardt KA, Sulzbacher I, Benesch T, Födinger M, Sunder-Plassmann G, Haas M. Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation. *Am J Transplant* 2007;7:2515-2521.

(17) Carlini RG, Rojas E, Weisinger JR et al. Bone disease in patients with long-term renal transplantation and normal renal function. *Am J Kidney Dis* 2000;36:160-166.

(18) Faugere M-C, Mawad H, Qi Q, Friedler R, Malluche HH. High Prevalence of Low Bone Turnover and Occurrence of Osteomalacia after Kidney Transplantation. *J Am Soc Nephrol* 2000;11:1093-1099.

(19) Delanaye P, Souberbielle JC, Lafage-Proust MH, Jean G, Cavalier E. Can we use circulating biomarkers to monitor bone turnover in CKD haemodialysis patients? Hypotheses and facts. *Nephrol Dial Transplant* 2014;29:997-1004.

(20) Frost ML, Compston JE, Goldsmith D et al. (18)F-fluoride positron emission tomography measurements of regional bone formation in hemodialysis patients with suspected adynamic bone disease. *Calcif Tissue Int* 2013;93:436-447.

(21) de Oliveira RB, Barreto FC, Custodio MR et al. Brazilian Registry of Bone Biopsy (REBRABO): design, data elements and methodology. *J Bras Nefrol* 2014;36:352-359.