Brazilian Registry of Bone Biopsy (REBRABO): design, data elements and methodology

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ABSTRACT

Introduction: Mineral bone disorder (MBD) is a common condition in chronic kidney disease (CKD) patients and causes significant morbidity and mortality. Data involving prevalence of alterations in bone histological patterns, impact of different treatments and its repercussion in outcomes, such as bone fractures, hospitalization, cardiovascular disease and mortality, are scarce. Data bank registry can be a valuable tool to understand epidemiological aspects of MBD CKD. The Brazilian Registry of Bone Biopsy (REBRABO) will be a national registry, coordinating by the Brazilian Society of Nephrology - Committee of MBD-CKD. **Objective:** To describe REBRABO´s design, elements of data and methodology. **Methods:** Will be an online national observational and multicentric data registry divided in two phases (retrospective, 1st phase) and prospective (2nd phase), including information from bone tissue histomorphometric analysis and demographics, clinical and laboratorial data from CKD-MBD patients. **Results:** The REBRABO´s first phase will explore data on demographics, clinical, laboratorial and bone histomorphometric analysis data from January/1986 to December/2013. The first results are expected in early 2015. **Conclusion:** Studies in the field of CKD-MBD are needed, particularly those analyzing its prevalence, associations between demographic, clinical, histological parameters, and major outcomes. The REBRABO will be a unique retrospective and prospective research platform including bone biopsy data in CKD-MBD patients.

Keywords: bone diseases; electronic health records; renal insufficiency, chronic.

INTRODUCTION

Mineral and bone disorders (MBD) are frequent in patients with chronic kidney disease (CKD) and they increase morbidity and mortality in these patients.[1] These disorders are known by the CKD-MBD acronym and encompass biochemical changes, vascular and soft tissue calcifications, and renal osteodystrophy (RO), which makes up the bone diseases in CKD patients.[2]

Knowledge on the pathophysiology, diagnosis and treatment of CKD-MBD has increased substantially in recent decades.[3-6] Despite the advent of new bone remodeling biochemical markers,[7,8] bone biopsy is still considered the gold standard for RO diagnosis.[2,9] In Brazil, few laboratories analyze bone tissue without prior decalcification, with bone remodeling quantification by histomorphometry. It is estimated that in the last 30 years, around 5,000 patients with CKD-MBD were studied employing this technique. These biopsies were analyzed mainly at the University of São Paulo (USP) and Federal University of São Paulo (UNIFESP), providing a wealth of data that needs to be computerized, processed and made available to the scientific community.

There are few studies in the literature that assess the prevalence of different types of RO, as well

as the impact of treatment and its effects on outcomes such as fractures, hospitalization, cardiovascular disease and mortality. In our setting, one study assessed the types of RO in 2,340 patients with stage 5D CKD (93.1% in hemodialysis), from 1985 to 2001.[10] The results of this study showed an increased prevalence of secondary hyperparathyroidism related to bone disease and reduced prevalence of aluminum-intoxication in the 90s compared to the 80s.

New guidelines for the diagnosis and treatment of CKD-MBD were introduced in recent years, changing previously established paradigms.[11-13] The prevalence of different types of RO has been modified over the last decade, especially the increased prevalence of static bone disease.[14-16] However, more studies are needed for understanding the pathophysiology of CKD-MBD, its complications and the impact of therapy, with the goal of contributing to quality of life improvement and reducing the high mortality rates of these patients.

Within this context it is necessary to create records that identify the different types of RO, risk factors, symptoms and complications associated with these disorders. The Brazilian Registry of Bone biopsies (REBRABO) will be a national, multicentric, observational database, coordinated by the Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) Committee of the Brazilian Society of Nephrology (SBN). This register will examine demographic, clinical, laboratorial and histomorphometric parameters from bone tissue of patients with CKD-MBD retrospectively and prospectively.

REBRABO's primary mission will be to identify associations between variables mentioned and their relationships with clinical outcomes. This information will serve as a research platform to expand the knowledge about CKD-MBD.

The main objectives of REBRABO are:

- Create a database with national multicentric information from CKD-MBD patients as to changes found in bone biopsies;
- Obtain data on the demographic, clinical and laboratorial characteristics of patients submitted to bone biopsy;
- Identify associations between CKD-MBD and clinical outcomes, including mortality, fractures, hospitalizations and quality of life;
- Propose new guidelines for CKD-MBD diagnosis and treatment, aiming at quality of life and survival improvements.

Database and methods

REBRABO will be a database containing demographic, clinical and laboratorial data on CKD-MBD patients submitted to bone biopsy, as well as the results of these biopsies.

Data will be added by electronic means only, online, via a website physically located in computers at the private data center, contracted for this purpose (e.g., Locaweb). The database is programmed in "PHP" languages (Hypertext preprocessor), "JavaScript", "HTML" (Hypertext Markup Language) and "Css" (Cascading Style Sheets), and is managed by MySQL system. Such data inclusion is to be performed by licensed physicians only, previously registered in the SBN or REBRABO database or through user authentication via individualized password.

Initially (retrospective phase), we analyzed data from patients submitted to bone biopsies between 1986 and 2013, which processing and reports were carried out by the Kidney Hospital Bone Histomorphometry Labs/Oswaldo Ramos Foundation, Federal University of São Paulo (UNIFESP), São Paulo, Brazil, and Bone Histomorphometry Laboratory of the Kidney Pathophysiology - LIM-16, School of Medicine, University of São Paulo, São Paulo, Brazil. In the prospective phase we included patients whose bone biopsies were indicated by their

physicians, or patients who participated in clinical trials approved by a medical ethics and research committee. There will be no REBRABO interference on the indication of bone biopsy, or treatment of any patient.

These data will be organized and scanned according to a standard electronic form (Table 1, Figure 1, Appendices 1, 2 and 3). When the bone tissue analysis report becomes available, it will be included in REBRABO through a standard electronic form (Figure 2 and Appendix 4). For data analysis, researchers may use filters to exclude records that do not meet the specific criteria of each research.

To increase the communication potential and facilitate scientific research, REBRABO will adopt the terminology recommended by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, through the TMV classification [Turnover Mineralization and Volume].[2] Quantitative histomorphometric data, when available, will be grouped according to the structural parameters of formation, resorption and mineralization, which nomenclature follows the standards of the American Society for Bone and Mineral Research (ASBMR)[17] (Tables 2 and 3).

REBRABO data will be validated before its analysis. This process will take place by the very program structure, which will control data inclusion, preventing incorrect data entry. We have to bear in mind that all records will be checked by two different observers with experience in clinical research.

Data analysis will be descriptive and plotted on a frequency table for categorical and analytical variables, continuous variables which will be represented as mean ± standard deviation or as median and interquartile ranges, as appropriate. Groups with normal distribution will be compared using the Student *t*-test or ANOVA; and the Mann-Whitney or Kruskal-Wallis tests for groups with non-parametric distribution. Categorical variables will be analyzed using the chi-square or Fisher test. Correlation analysis between continuous variables will be made by the Pearson (parametric data) or Spearman (nonparametric data) tests. Statistical analysis will be performed using the SPSS software version 17.1. The $p < 0.05$ value will be considered statistically significant.

Data use and sharing

Researchers outside the CKD-MBD SBN committee can access REBRABO data upon request to the aforementioned Committee, through a standardized form. Applicants must sign a document accepting the use of data, confidentiality and publications terms and destruction of data after use. No data from REBRABO will be provided without signing this term of acceptance and work plan approval, or before the main analyses and publications from the CKD-MBD SBN Committee.

Table 1 REBRABO data collection instruments

Document Description
Demographic/Clinical Census
(Appendix 1) Form used to collect demographic characteristics and clinical information from each patient. We will collect data such as age, gender, ethnicity, CKD etiology, kidney disease duration, time in dialysis, dialysis mode, comorbidities, history of fractures, cardiovascular events, and others.
Laboratorial census
(Appendix 2) Form used to collect laboratorial information in the last 6 months related to the bone biopsy date, including the following tests: ion calcium and/or total; phosphorus; alkaline phosphatase - total or bone fraction, parathyroid hormone(PTH); 25(OH)-vitamin D; creatinine; urea; hemoglobin; hematocrit; platelets; leucocytes; albumin; ferritin; aluminum; and others.
Bone tissue data analysis
(Appendix 3) Form used to collect information on bone histology according to quantitative and semiquantitative histomorphometric parameters (Table 3 and Appendix 3).

CKD: Chronic kidney disease.

Figure 1. Standard electronic form for data entry from the Demographic/Clinical Census.

Figure 2. Standard electronic form for data entry related to the reports from the bone tissue analysis.

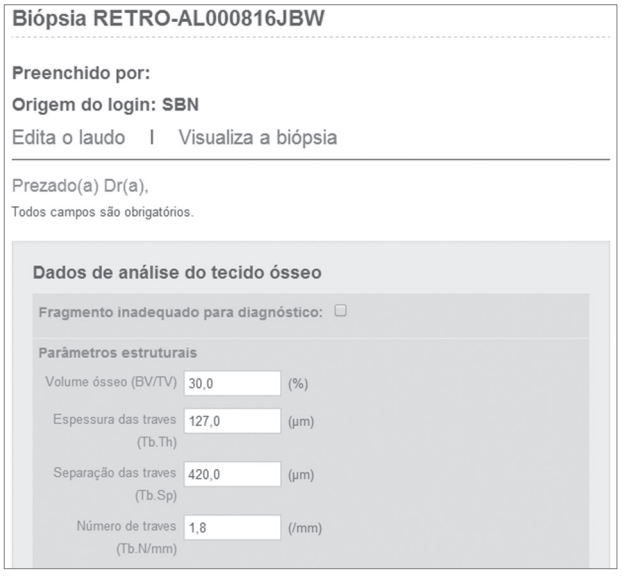

Table 2 TMV classification system

Parameters	Classification		
Turnover (R)	low	normal	high
Mineralization (M)	normal	abnormal	NA
Volume (V)	reduced	normal	high

T: Turnover; M: Mineralization; V: Volume; NA: Not applicable.

Protection of research subjects

The coordinator of the REBRABO will send data to the participating center preserving the patient's identity. There will not be any form of influence on patient bone biopsy or treatment indications, emphasizing that this database is only observational. It's up to each physician participating in REBRABO to obtain the consent of each patient, as well as signing and keeping the patient's signed informed consent (IC) form for data inclusion in REBRABO.

Table 3 Structural patterns of bone formation, resorption and mineralization from the bone tissue histomorphometric analyses

Structural parameters	unit
Bone volume	(BV/TV) %
Bone ridges thickness	(Tb.Th) µm
Ridges separation	(Tb.Sp) µm
Number of bone ridges	(Tb.N/mm)/mm
Formation parameters	
Osteoid volume	(OV/BV) %
Osteoid thickness	(O.Th) µm
Osteoid surface	(OS/BS) %
Osteoblastic surface	(Ob.S/BS) %
Resorption parameters	
Resorption surface	(ES/BS) %
Osteoclastic surface	(Oc.S/BS) %
Mineralization parameters	
Mineralizing surface	(MS/BS) %
Mineral settling rate	(MAR) µm/day
Bone formation rate	(BFR/BS) $\mu m^3/\mu m^2$/day
Corrected bone formation rate	(Aj.AR) µm/day
Mineralizing time interval	(Mlt) day
Medullary fibrosis	
Fibrosis volume	(Fb.V) %
Metal deposits	
Aluminum-covered surface	(Al.S/BS) %
Iron-covered surface	(Fe.S/BS) %

Conclusion

There is a paramount need for studies assessing the prevalence, associations between sociodemographic, clinical, laboratorial and bone-tissue histomorphometric variables and their relationships with clinical outcomes in the CKD-MBD field. REBRABO will be one of the largest databases of bone biopsies from patients with BMD, especially associated with CKD, and will serve as a research platform for future studies in this field.

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Appendix 1 Demographic/clinical census form

Name: _____
CPF (If child, use the CPF from one of the parents): _____
Home phone #: _____ Cell phone #: _____
City: _____ State: _____
Patient's ID number at REBRABO: _____
Origin center: Name of the biopsy center: _____
Name of the professional in charge of adding the data:
Medical specialty that indicated the bone biopsy:
□ Nephrology □ Endocrinology □ Rheumatology □ Orthopedics
□ Other _____
Age (complete years): ___
Weight: __,_ kg Height: _,__ m
Residual clearance: __,_ ml/min
Gender:
□ Male □ Female

Continued Appendix 1.

Ethnicity:			
□ White	□ Black	□ Brown	□ Yellow
□ Indigenous	□ Other _____		
Bone biopsy indication:			
□ Atraumatic fracture	□ Persisting bone pain	□ Hyperphosphatemia and/or unexplained hypercalcemia	□ Possible aluminum intoxication
□ Pre-parathyroidectomy	□ Pre osteoporosis therapy	□ Clinical study	□ Other
Bone biopsy date: _____(dd/mm/yyyy)			
CKD etiology:			
□ Hypertension	□ *diabetes mellitus*	□ Chronic glomerulonephritis	□ Chronic pyelonephritis
□ Polycystic kidney disease	□ Kidney stones	□ Congenital nephropathy	□ Hereditary nephropathy
□ Undetermined	□ Other: _____	□ None	
Time of kidney disease (months): ___ □ Unknown			
Time in dialysis (months): ___ □ Unknown			
Dialysis mode:			
□ Hemodialysis □ Peritoneal dialysis - CAPD □ Peritoneal dialysis - APD			
Current kidney transplant:			
□ No □ Yes, duration (0 to 360 months): _____			
Previous kidney transplant:			
□ No □ Yes, duration (0 to 360 months): _____ □ Unknown			
Comorbidities:			
□ Hypertension	□ *diabetes mellitus*	□ Dyslipidemia	□ Coronary disease
□ Smoking	□ Obesity	□ Malnutrition	□ Chronic inflammatory disease
□ Menopause	□ Peripheral arterial hypertension	□ Hepatitis C	□ Mineral bone disorder complication in CKD
□ Neoplasia	□ None	□ Other: _____	
Bone pain intensity reported by the patient (visual analogue):			
□ 0: no pain	□ 1	□ 2	□ 3
□ 4	□ 5: maximum pain		
Other signs and symptoms:			
Weakness:	□ No	□ Yes	
Tendon rupture:	□ No	□ Yes	
Deformities:	□ No	□ Yes	
Pruritus:	□ No	□ Yes	
Red eye:	□ No	□ Yes	
Myalgia:	□ No	□ Yes	
Skin lesion:	□ No	□ Yes	
Fracture:	□ No	□ Yes	
Personal medical history:			
□ Parathyroidectomy	(dd/mm/yyyy)	Type: ____	
□ Bone biopsy	(dd/mm/yyyy)		
□ Atraumatic bone fracture	□ Aluminum intoxication	□ Acute myocardial infarction	□ Cerebral vascular accident
□ None	□ Other: ___		

Continued Appendix 1.

Medications in current use:			
□ Calcium carbonate	□ Calcium acetate	□ Sevelamer hydrochloride	□ Sevelamer carbonate
□ Calcitriol PO	□ Calcitriol IV	□ Paricalcitol	□ D3 or D2 Vitamin
□ Cinacalcet	□ Bisphosphonate	□ Corticosteroids	□ Dicumarinic
□ Carbamazepine	□ Deferoxamine	□ None	□ Other

Appendix 2 Laboratorial census form laboratorial census form

Fill out the results from the blood workup, using the bone biopsy date as a reference (inform the result closest to the bone biopsy date)
Ion calcium: _____ unit: __/__
Total calcium: _____ (mg/dl):
Phosphorus: _____ (mg/dl):
Parathyroid hormone (PTH): _____ (pg/ml)
Total alkaline phosphatase: _____ (UI/l):
Alkaline phosphatase bone fraction: _____ (UI/l or %)
Albumin: _____ (g/dl):
25(OH)-vitamin D: _____ (ng/ml)
Creatinine:_____ (mg/dl)
Urea: _____ (mg/dl)
Hemoglobin: _____ (g/dl)
Hematocrit: _____ (%)
Ferritin: _____ (mg/dl)
C-Reactive Protein: _____ (mg/dl)
Bicarbonate: _____ (mmol/l)
Aluminum: _____ (µg/L)
B2 microglobulin: _____ (ng/ml)

Appendix 3 Image exams census form

Radiographies: (Classify the type of disorder as localized or diffuse)
Radiographies □ No □ Yes
Vascular calcification □ No □ Yes, Type: _____
Fracture signs □ No □ Yes
Signs of resorption □ No □ Yes, Type: _____
Osteopenia □ No □ Yes, Type: _____
Signs of brown tumor □ No □ Yes
Bone deformities □ No □ Yes
Bone densitometry:
Osteoporosis:
□ No □ Yes
Osteopenia:
□ No □ Yes
Parathyroid scintigraphy:
Signs of hyperparathyroidism:
□ No □ Yes
Positive uptake in:
□ Right upper pole □ Left upper pole □ Right lower pole □ Left lower pole

Continued Appendix 3.

Parathyroid ultrasound scan:
Signs of hyperparathyroidism:
□ No □ Yes Number of glands found: __

Appendix 4 Bone tissue analysis data

□ Fragment inadequate for the diagnosis			
Structural parameters:			
Bone volume (BV/TV): __,_%	Bone trabeculae thickness (Tb.Th): __,_µm	Bone trabeculae separation (Tb.Sp): __,_µm	Number of bone trabeculae (Tb.N/mm): __,_/mm
Forming parameters			
Osteoid volume (OV/BV): __,_% Osteoid thickness (O.Th): __,_µm Osteoid surface (OS/BS): __,_% Osteoblastic surface (Ob.S/BS): __,_%			
Resorption parameters			
Resorption surface (ES/BS): __,_% Osteoclastic surface (Oc.S/BS): __,_%			
Mineralization parameters			
Mineralizing surface (MS/BS): __,_% Mineral deposition rate (MAR): __,_µm/day Bone formation rate (BFR/BS): __,_μ^3/μ^2m/day Corrected bone formation rate (Aj.AR): __,_µm/day Mineralization time interval (Mlt): __,_days			
Fibrosis:			
Fibrosis volume (Fb.V): __,_%			
Metal deposits:			
Aluminum-coated surface (Al.S/BS): __,_% Iron-coated surface (Fe.S/BS): __,_% Report (semiquantitative analysis): _____ _____ _____ _____			
Remodeling, mineralization and volume (RMV):			
Remodeling:	□ High (+1)	□ Medium (0)	□ Low (-1)
Mineralization:	□ Normal (0)	□ Abnormal (99)	
Volume:	□ High (+1)	□ Normal (0)	□ Reduced (-1)
Aluminum intoxication:	□ No	□ Yes (if > 30%)	
Iron intoxication:	□ No	□ Yes	