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RENAL OSTEODYSTROPHY AND CLINICAL OUTCOMES: A PROSPECTIVE COHORT STUDY

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Brief Communication

RENAL OSTEODYSTROPHY AND CLINICAL OUTCOMES: A PROSPECTIVE COHORT STUDY

Short title: ROD and outcomes

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The results presented in this paper are related in part to those previously published by the same first and senior authors (references numbers 4, 6, and 7). This study was presented, in part, at the ERA-EDTA 2023, 60th European Renal Association Congress, 15th-18th June 2023, Milan, Italy (reference number 8).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

This study was conceived by RBO and CEMC. The data were generated by CEMC, NAVB, KRSQ, LMR, and VJ. The data were analyzed by CEMC, JB, and RBO. VJ and RBO analyzed all bone samples. Significant intellectual content was given by CEMC, RBO, ABC, ACS, and VJ. All authors contributed to the interpretation of the data and revision of the manuscript. All authors have approved the final version of the article uploaded to the journal website.

ABSTRACT

Introduction: Renal osteodystrophy (ROD) refers to a group of bone morphological patterns that derive from distinct pathophysiological mechanisms. Whether ROD subtypes influence long-term outcomes are unknown. Our objective was to explore the relations between ROD and outcomes. **Methods:** This study is a subanalysis of the Brazilian Registry of Bone Biopsies (REBRABO). The samples from individual patients were classified as having osteitis fibrosa (OF), mixed uremic osteodystrophy (MUO), adynamic bone disease (ABD), osteomalacia (OM), normal/minor alterations, and according to Turnover/Mineralization/Volume (TMV) system. Patients were followed for 3.4 yrs. Adjudicated events were: bone fractures, hospitalization, major adverse cardiovascular events (MACE), and death. **Results:** We enrolled 275 participants, 248 (90%) of them on dialysis. At follow-up, 28 bone fractures, 97 hospitalizations, 44 MACE, and 70 deaths were recorded. ROD subtypes were not related to outcomes. **Conclusion:** The incidence of clinical outcomes did not differ between the types of ROD.

Keywords: Chronic Kidney Disease-Mineral and Bone Disorder; Renal Osteodystrophy; Renal Insufficiency, Chronic; Clinical Outcomes.

RESUMO

Introdução: Osteodistrofia renal (OR) refere-se a um grupo de padrões morfológicos ósseos que decorrem de mecanismos fisiopatológicos distintos. É desconhecido se os subtipos de OR influenciam desfechos em longo prazo. Nosso objetivo foi explorar as relações entre OR e desfechos. **Métodos:** Este estudo é uma subanálise do Registro Brasileiro de Biópsias Ósseas (REBRABO). As amostras de cada paciente foi classificadas em osteíte fibrosa (OF), osteodistrofia urêmica mista (MUO), doença óssea adinâmica (ABD), osteomalácia (OM), alterações normais/menores, e pelo sistema Remodelação/Mineralização/Volume (RMV). Os pacientes foram acompanhados por 3,4 anos. Os eventos adjucados foram: fraturas ósseas, hospitalizações, eventos cardiovasculares adversos maiores (MACE), e morte. **Resultados:** Analisamos 275 indivíduos, 248 (90%) deles estavam em diálise. No seguimento, 28 fraturas ósseas, 97 hospitalizações, 44 MACE e 70 mortes foram registradas. Os subtipos de OR não foram relacionados aos desfechos. **Conclusão:** A incidência de desfechos clínicos não diferiu entre os tipos de OR.

Palavras-chave: Distúrbio Mineral e Ósseo na Doença Renal Crônica; Osteodistrofia Renal; Insuficiência, Renal Crônica; Desfechos Clínicos.

INTRODUCTION

Renal osteodystrophy (ROD) refers to a group of bone morphological changes due to chronic kidney disease (CKD) that are classically classified as osteitis fibrosa, mixed uremic osteodystrophy, adynamic bone disease, and osteomalacia, and/or by Turnover / Mineralization / Volume (TMV) system.[1]

Each one of these patterns is not only histologically different but also derive from distinct pathophysiological mechanisms.[1,2] For example, differences in bone turnover, which is a classifying feature of ROD variety, may influence vascular calcification and hence the risk of cardiovascular disease, the leading cause of death among CKD subjects.[3]

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The hypothesis that the ROD variety may influence the incidence of outcomes was previously tested by our group, at relatively short mean follow-up.[4] Nevertheless, whether ROD subtypes are evenly related to long-term outcomes is unknown.

To tackle this unmet need, we hereby present the results of a subanalysis of the *Brazilian Registry of Bone Biopsy* (REBRABO),[5] in which patients with ROD were followed by 3.4 years and hard outcomes were adjudicated. Noteworthy, to the best of our knowledge this is the first study to assess the influence of ROD subtypes on long-term morbimortality.

METHODS

This study was conducted as a subanalysis of the REBRABO,[5] and is related in part to those previously published.[4,6-8] The detailed methodology has already been described elsewhere.[4-8] Briefly, the REBRABO is a prospective cohort of patients with ROD. This research was carried out during the period from Aug-15 to Dec-21. The bone samples from patients with CKD were classified as having osteitis fibrosa (OF), mixed uremic osteodystrophy (MUO), adynamic bone disease (ABD), osteomalacia (OM), normal/minor alterations, and according to Turnover/Mineralization/Volume (TMV) system. Patients were followed for 1242 (693-1508) days, or 3.4 yrs. Adjudicated events were bone fractures, hospitalization, major adverse cardiovascular events (MACE; unstable angina, nonfatal acute myocardial infarction, elective or emergency coronary revascularization, transient ischemic attack, stroke, and cardiovascular death), and death. Cox regression analysis was employed to detect covariates and factors associated with outcomes. The study was approved by the ethics committee (number 4131141.6.0000.5404), and patients provided their written consent.

RESULTS

We enrolled 275 patients in this subanalysis, 248 (90%) of them on dialysis. OF was diagnosed in 113 (41%) patients, ABD in 79 (29%), MUO in 59 (21%), OM in 12 (4%), and normal/minor alterations in 12 (4%). Table 1 shows the characteristics of the patients at baseline according to the main outcome recorded at follow-up. Of note, patients who were lost to follow-up (N = 111) had similar characteristics to the sample of this subanalysis (Table S1).

At follow-up, 28 bone fractures, 97 hospitalization events, 44 MACE, and 70 deaths were recorded, corresponding to an annual incidence of 4.4%, 14.6%, 6.8%, and 7.5%, respectively. The proportion of ROD types was similar according to the outcomes (Table 2).

Patients who presented bone fractures have similar characteristics comparing those patients without. Patients who presented hospitalization were older [52 (47-60) *vs*. 48 (40-58) yrs.; p=0.03], and presented low serum hemoglobin levels [11.5 (10-13) *vs*. 12.2 (10.7-13.7; p=0.02]. Low serum hemoglobin levels were independently associated with hospitalization [OR: 0.903 (CI: 0.823-0.991)]. Patients who presented MACE have lower serum hemoglobin levels [11.1 (9.6-12.6) *vs*. 12 (10.8-13.5; p=0.026], increased prevalence of DM [11 (25%) *vs*. 15 (10%); p=0.01], and previous CVD [8 (18%) *vs*. 8 (5%); p=0.008]. DM was an independent predictor for MACE [OR: 3.287 (CI: 1.541-7.011)].

Compared to survivors patients who died were older [56 (50-64) *vs*. 50 (41-58) yrs.; p<0.0001], had increased prevalence CVD [13 (19%) *vs*. 14 (7%); p=0.004], lower proportion of phosphate in reference range [17 (24%) *vs*. 80 (39%), p=0.026] and lower proportion of parathyroidectomy [6 (9%) *vs*. 40 (19%); p=0.03]. Age, previous CVD, and proportion of serum phosphate levels out of the reference range were independent predictors for death [OR: 1.046 (CI: 1.024-1.069), p=0.0001; OR: 1.856 (CI: 1.009-3.413), p=0.04; OR: 1.942 (CI: 1.116-3.379), p=0.019; respectively].

Different models of Cox regression analysis adding OF, MUO, ABD, OM, or bone TMV parameters did not reveal ROD as an independent predictor for hospitalization, MACE, or death (Figure 1).

DISCUSSION

In summary, we observed an annual incidence of bone fractures, hospitalization, MACE, and death of 4.4%, 14.6%, 6.8%, and 7.5%, respectively. The incidence of adjudicated outcomes did not differ according to ROD types.

Compared to our previous report[4] the follow-up time was doubled, and the number of patients increased from 115 to 275. However, we did not detect the effects of different patterns of ROD on these outcomes.

Brazilian Journal of Nephrology
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Of note, the annual incidence of death in this cohort (7.5%) is lower than that reported by national surveys, which registered an average estimated annual crude mortality rate of dialysis patients of about 19%, in the last 5 years.[9] This data may suggest that bone histology of patients with ROD can impact clinical decisions, and may be associated with lower death rates.

This study has limitations to acknowledge. This is an essentially descriptive study and is not a random analysis. The impact of treatments based on ROD diagnosis on outcomes was not measured, and the extrapolation of these findings to other populations is uncertain. Nephrologists in charge of each patient indicated and performed the bone biopsy on their own understanding, or due to research protocol. Also, they entered baseline data in REBRABO-system. Outcomes were adjudicated by telephone calls with the dialysis unit's staff, and the patients. These facts constitute unavoidable bias. Our study has strengths: prospective cohort studies enrolling patients with ROD are scarce. Our study is the first to access the effects of ROD on hard outcomes, with a rather long follow-up.

CONCLUSIONS

In this prospective cohort, the incidence of adjudicated outcomes did not differ between the patterns of ROD.

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Table 1. Characteristics of the patients at baseline according to the main outcome recorded at follow-up.

	All (N = 275)	Survivors (N = 205)	Deceased (N = 70)	p
Age (years)	52 (42–60)	50 (41 – 58)	56 (50–64)	**0.0001**
BMI (kg/m^2)	24.1 (22–27)	24.7 (22–27)	24 (22–27)	0.92
Male (N, %)	143 (52)	104 (51)	39 (56)	0.47
Caucasian (N, %)	118 (43)	86 (42)	32 (46)	0.58
DM (N, %)	39 (14)	25 (12)	14 (20)	0.10
Previous PTx (N, %)	46 (17)	40 (19)	6 (9)	**0.03**
Previous CVD (N, %)	27 (10)	14 (7)	13 (19)	**0.004**
CKD etiology				0.05
AH (N, %)	78 (28)	59 (29)	19 (27)	
CGN (N, %)	65 (24)	51 (25)	14 (20)	
DM (N, %)	37 (13)	21 (10)	16 (23)	
Dialysis vintage (months)	84 (36–146)	84 (36–144)	77 (38–171)	0.83
Hemodialysis (N, %)	221 (80)	165 (90)	56 (86)	0.37
Hemoglobin (g/dL)	11.5 (10.3–13)	11.6 (10.3–13.2)	11.2 (10.3–12.1)	0.06
Total calcium (mg/dL)	9.3 (8.6–9.8)	9.3 (8.6–9.9)	9.2 (8.8–9.8)	0.93
Phosphate (mg/dL)	5 (3.9–6.5)	4.9 (3.9–6.3)	5.1 (3.7–6.5)	0.91
Parathormone (pg/mL)	234 (65–733)	238 (58–752)	217 (82–544)	0.97
Alkaline phosphatase (IU/L)	129 (79–217)	118 (76–211)	132 (83–239)	0.27
25-vitamin D (ng/mL)	29.6 (20.5–38)	31 (22–38)	26.3 (19.2–35.8)	0.39

BMI, body mass index; DM, Diabetes *Mellitus*; PTx, parathyroidectomy; CVD, cardiovascular disease; AH, arterial hypertension; CGN, chronic glomerulonephritis.

Table 2. The proportion of renal osteodystrophy, and the incidence of clinical outcomes.

Renal osteodystrophy diagnosis	Bone fracture			Hospitalization			MACE			Death		
	No	Yes	p	No	Yes	p	No	Yes	p	No	Yes	p
Osteitis fibrosa (N; %)	64 (41)	14 (50)	0.36	43 (43)	38 (39)	0.54	62 (42)	17 (39)	0.62	87 (42)	26 (37)	0.43
Mixed uremic osteodystrophy (N; %)	26 (17)	7 (25)	0.28	17 (17)	20 (21)	0.54	24 (17)	9 (20)	0.63	42 (20)	17 (24)	0.50
Adynamic bone disease (N; %)	51 (32)	7 (25)	0.43	28 (28)	34 (35)	0.30	46 (32)	14 (32)	0.99	57 (28)	22 (31)	0.56
Osteomalacia (N; %)	6 (4)	0 (0)	NA	4 (4)	2 (2)	0.68	4 (3)	2 (4)	0.62	9 (4)	3 (4)	1.0
Normal/Minor alterations (N; %)	10 (6)	0 (0)	NA	7 (7)	3 (3)	0.33	8 (5)	2 (4)	1.0	10 (5)	2 (3)	0.73

MACE, major adverse cardiovascular events; NA, non-applicable.

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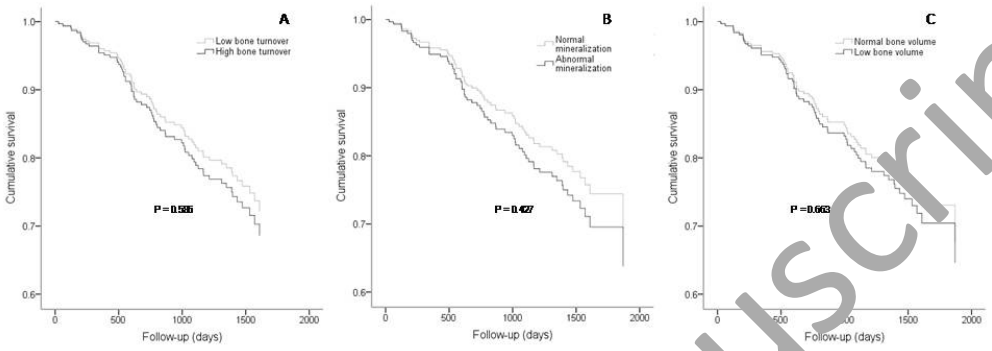
Figure 1. Effects of bone turnover, mineralization, and volume on death outcome.

Cox regression analysis survival curves for death outcome. Variables tested in the models: age, previous cardiovascular disease, previous parathyroidectomy, proportion of patients out of the reference range for serum phosphate levels, plus: bone turnover in (A), bone mineralization in (B), or bone volume in (C). Overall p = 0.0001.



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Brazilian Journal of Nephrology
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SUPPLEMENTAL FILE

Table S1. General and biochemical data according to follow-up.

	With follow-up (N = 275)	Lost follow-up (N = 111)	p
Age (years)	52 (42–60)	50 (39 – 60)	0.38
BMI (kg/m^2)	24.1 (22–27)	24 (21-27)	0.44
Male (N, %)	143 (52)	55 (49)	0.66
Caucasian (N, %)	118 (43)	42 (38)	0.36
DM (N, %)	39 (14)	18 (16)	0.61
Previous CVD (N, %)	27 (10)	9 (8)	0.60
Previous PTx (N, %)	46 (17)	27 (24)	0.08
CKD etiology			0.31
AH (N, %)	78 (28)	27 (24)	
CGN (N, %)	65 (24)	29 (26)	
DM (N, %)	37 (13)	9 (8)	
Dialysis vintage (months)	84 (36–146)	96 (51-168)	0.17
Hemodialysis (N, %)	221 (80)	94 (96)	0.06
Hemoglobin (g/dL)	11.5 (10.3–13)	11.5 (10-13)	0.77
Total calcium (mg/dL)	9.3 (8.6–9.8)	9.3 (8.6-10.1)	0.70
Phosphate (mg/dL)	5 (3.9–6.5)	4.8 (3.6-6)	0.15
Parathormone (pg/mL)	234 (65–733)	220 (55-930)	0.49
Alkaline phosphatase (IU/L)	120 (79–217)	129 (82-257)	0.20
25-vitamin D (ng/mL)	29.6 (20.5–38)	28.2 (22.2-36.6)	0.89

BMI, body mass index; DM, Diabetes *Mellitus*; PTx, parathyroidectomy; CVD, cardiovascular disease; AH, arterial hypertension; CGN, chronic glomerulonephritis.