Bone 91 (2016) 75–80

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

The pitfall of treating low bone turnover: Effects on cortical porosity

Maria Julia C.L.N. Araujo [a], Cristina Karohl [b], Rosilene M. Elias [a], Fellype C. Barreto [c,f], Daniela Veit Barreto [c], Maria Eugenia F. Canziani [d], Aluizio B. Carvalho [d], Vanda Jorgetti [a], Rosa M.A. Moyses [a,e,*]

[a] Nephrology Division, Universidade de São Paulo, São Paulo, Brazil
[b] Nephrology Division, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
[c] Nephrology Division, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil
[d] Nephrology Division, Universidade Federal de São Paulo, São Paulo, Brazil
[e] Medicine Master Degree Program, Universidade Nove de Julho, UNINOVE, São Paulo, Brazil
[f] Nephrology Division, Universidade Federal do Paraná, Curitiba, Brazil

ARTICLE INFO

Article history:
Received 19 January 2016
Revised 18 April 2016
Accepted 13 July 2016
Available online 15 July 2016

Keywords:
Cortical bone
Bone biopsy
Hemodialysis
Parathyroid hormone
Mineral metabolism

ABSTRACT

Although it is recognized that cortical bone contributes significantly to the mechanical strength of the skeleton, little is known about this compartment from bone biopsy studies, particularly in CKD patients. In addition, there is no prospective data on the effects of CKD-MBD therapy on cortical porosity (Ct.Po). This is a post hoc analysis on data from a randomized controlled trial on the effects of different phosphate binders on bone remodelling. Therapy was adjusted according to the first biopsy, and included sevelamer or calcium acetate, calcitriol and changes in calcium dialysate concentration. We measured Ct.Po at baseline and one year after. Fifty-two patients (46 ± 13 years old, 67% women and 60% white) were enrolled. Ct.Po was already high at baseline in 85% of patients [30% (17, 46)] and correlated with PTH ($p = 0.001$). Low bone turnover was seen in 28 patients (54.9%). After one-year treatment, PTH increased in patients with low turnover, as intended. However, increased Ct.Po was seen in 49 patients (94%). This increase correlated with the delta of phosphate ($p = 0.015$) and the delta of PTH ($p = 0.03$); it was also higher among non-white patients than in white patients ($p = 0.039$). The risk of increase in Ct.Po was 4.5 higher among non-white patients. Adjusted multiple regression analysis showed that the delta of Ct.Po was dependent on delta PTH and race ($r^2 = 0.193$). We concluded that in an attempt to increase bone turnover, the increase in PTH levels might be associated with higher cortical porosity, particularly in non-white patients. Whether this finding leads to a high risk of fracture deserves further investigation.

1. Introduction

It is well recognized that chronic kidney disease (CKD) patients are exposed to a high risk of fracture. Fractures are indeed associated with significantly higher morbidity and mortality in these patients than in the general population [1,2]. Compromised bone strength leading to fracture may be associated to changes in both trabecular and cortical bone compartments. Although it is well recognized that cortical bone contributes significantly to the mechanical strength of the skeleton, little is known about this compartment from bone biopsy studies.

Recently, it has been described that an increase in cortical porosity (Ct.Po) is a common finding in CKD, especially in non-white patients [3]. Moreover, a prospective study using high-resolution peripheral quantitative computed tomography has shown that CKD patients may experience deterioration in cortical bone over time [4].

Mineral bone disease (MBD) therapy is usually applied to control levels of phosphate, calcium and parathyroid hormone (PTH), including phosphate binders, calcitriol as well as adjustments in calcium dialysate concentration. However, there is paucity of data regarding the effects of such therapy on Ct.Po. Therefore, we have aimed to evaluate the effects of one-year CKD-MBD therapy on Ct.Po in patients on conventional hemodialysis.

2. Material and methods

2.1. Subjects and study design

This is a post-hoc analysis of a randomized clinical trial, the BRIC study [5], that has compared two phosphate binders, sevelamer and calcium acetate, in hemodialysis patients. The study protocol was reviewed and approved by the local institutional ethics board and all patients gave informed consent. Briefly, 101 subjects underwent a 1-year therapy with either sevelamer or calcium acetate. Baseline samples were drawn and bone biopsies were performed after a 2-week washout period, in which all phosphate binders and calcitriol were withheld. The

* Corresponding author at: Universidade Nove de Julho (UNINOVE), Rua Iperoig, 690 ap 121, Perdizes, 050016-000 São Paulo, SP, Brazil.
E-mail address: rosa.moyses@uol.com.br (R.M.A. Moyses).

http://dx.doi.org/10.1016/j.bone.2016.07.009
8756-3282/

study target goals comprised serum phosphate between 3.5 and 5.5 mg/dl, ionized calcium between 1.11 and 1.40 mmol/l, and PTH between 150 and 300 pg/ml. The doses used to achieve the target goals of PTH, calcium and phosphate were adjusted according to individual response and label recommendations of each drug (up to 12,000 mg daily for sevelamer, and up to 2028 mg of elemental calcium daily for calcium acetate). However, in patients that presented low bone turnover at baseline, even when baseline PTH was higher than 300 pg/ml, investigators were recommended to decrease the dialysate calcium concentration (d[Ca]) from 3.5 to 2.5 mEq/l, which was done in 24 patients; calcitriol was also withdrawn in these patients. Patients did not receive any vitamin D supplementation during the study. For the current study, as shown in Fig. 1, data from 52 patients was available for our analysis.

2.2. Bone biopsy

Bone biopsies were obtained from the iliac crest, using an electrical trephine, after pre-labeling with tetracycline (3 days) administered over 2 separated periods 10 days apart. Bone fragments were submitted to the usual processing and histologic studies [6]. Sections were stained with toluidine blue. Bone histomorphometry was conducted using the Osteomeasure software (Osteometrics Inc., Atlanta, Ga., USA). Static and dynamic parameters were analyzed in accordance with the Standards of the American Society of Bone and Mineral Research [7]. The references range (RR) used for static parameters were obtained from our normal laboratory controls [8], whereas the ranges for the dynamic parameters were the same as those described elsewhere [9]. Patients were classified into the following groups: (1) hyperparathyroid bone disease, defined as the bone formation rate (BFR/BS), plus either an osteoblast or osteoclast surface of >1 SD above the normal range, osteoid volume (OV/BV) within or above the normal range, and marrow fibrosis >0.5%; (2) adynamic bone disease (ABD), defined as BFR/BS and OV/BV of >1 SD below the normal range and marrow fibrosis <0.5%; (3) osteomalacia, defined as BFR/BS of >1 SD below the normal range plus OV/BV of >1 SD above the normal range, and (4) mixed renal osteodystrophy, defined as BFR/BS of >1 SD below the normal range, OV/BV and osteoblast surface of >1 SD above the normal range and narrow fibrosis ≧0.5%. Thereafter, bone histology was categorized according to the TMV classification [10]. Osteitis fibrosa (OF) and mixed uremic osteodystrophy were considered high-turnover diseases, whereas osteomalacia and ABD were considered low-turnover diseases. Cortical bone was assessed under 200 x magnifications using the Osteomeasure software by a histomorphometrist blinded to biochemical values. Cortical porosity between 1.9% and 10% was considered normal, as previously described [3].

2.3. Statistical analysis

Continuous data are presented as means ± SD unless indicated otherwise, and categorical data are presented as percentage. Student's *t*-test or Mann Whitney U tests were used to compare groups, according to normal or abnormally distributed variables. Changes from baseline to one-year follow-up, on biochemical and histomorphometric parameters, were compared by paired *t*-test or Wilcoxon matched test, as appropriate. Relationships between single variables were examined by Spearman correlation coefficient. Multivariable relationships between the delta of Ct.Po and independent variables (selected from univariate analyses) were also examined. All p values were two sided and values < 0.05 were considered significant. Analyses were performed with the use of SPSS 20.0.1 (SPSS Inc., Chicago, Ill).

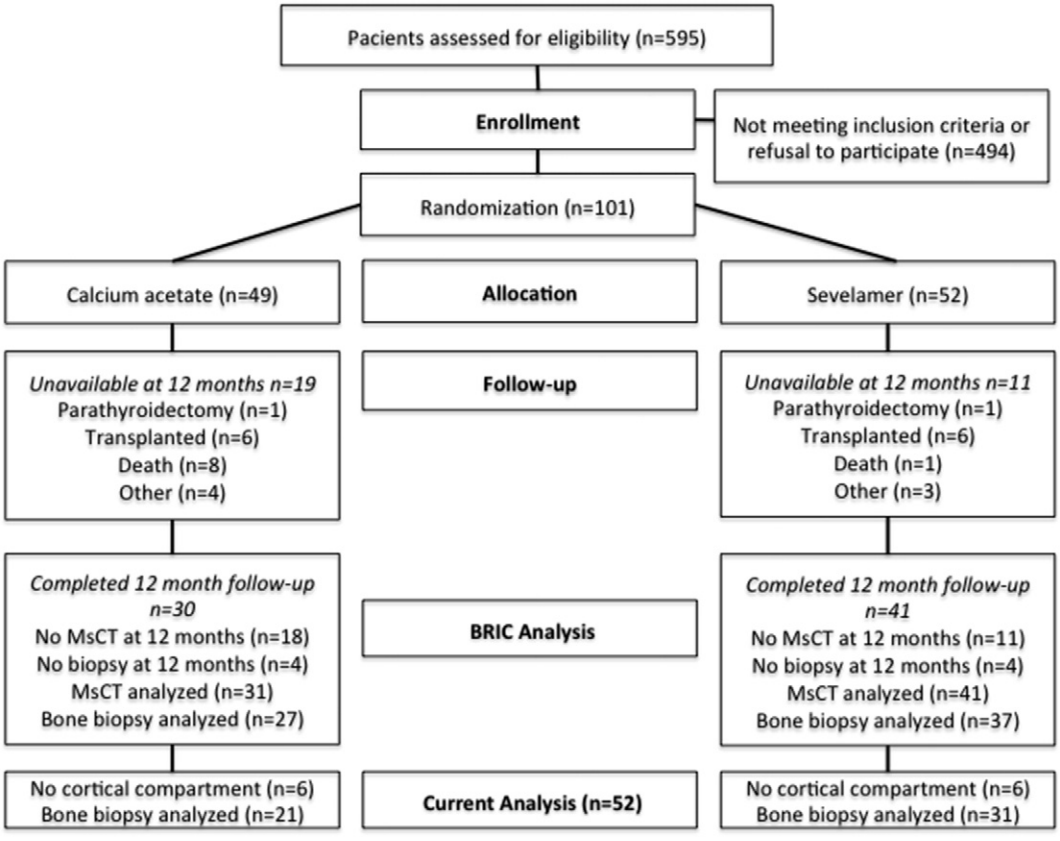

Fig. 1. Flow of participants showing a subset of patients from BRIC study that were included in the current study.