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).

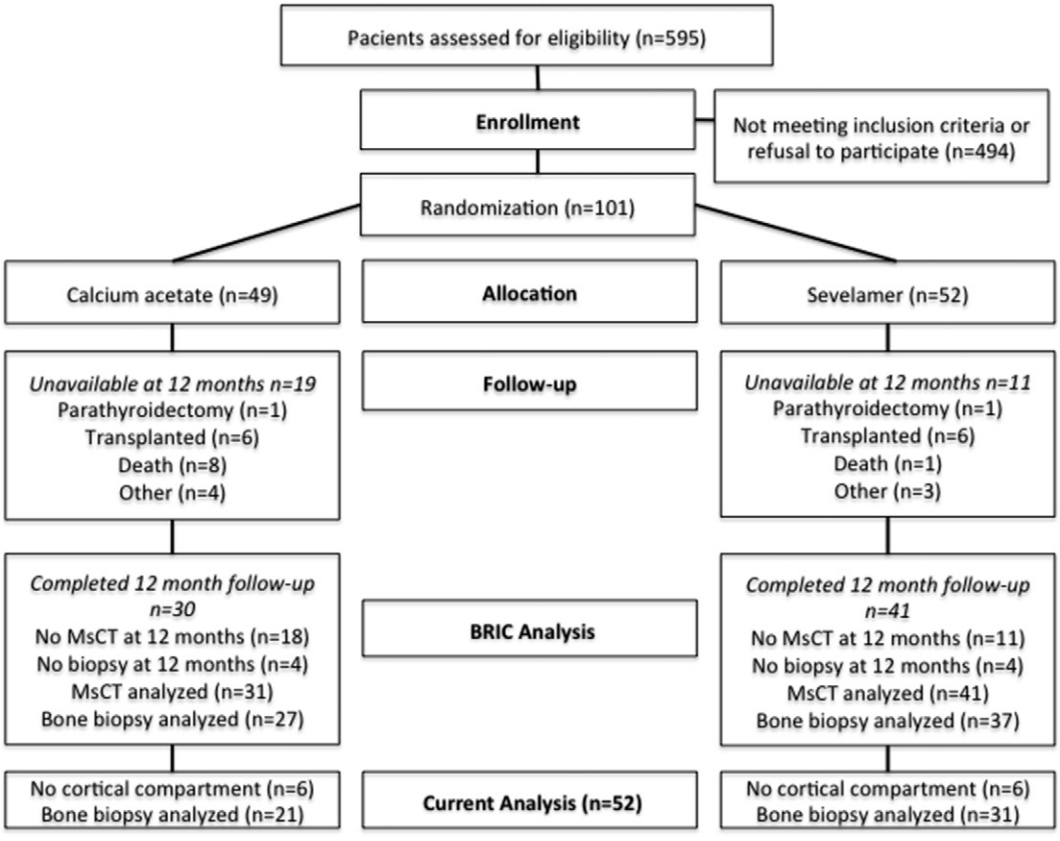

Fig. 1. Flow of participants showing a subset of patients from BRIC study that were included in the current study.

3. Results

3.1. Baseline data

The study sample was comprised of 52 patients, 67% women, and 60% white, with age 46 ± 13 years, on dialysis for 41 ± 26 months. Of note, only 7 patients (13%) were diabetic. Their biochemical and cortical bone parameters are shown in Table 1. Serum calcium and 25-vitamin D were within the normal range. As the patients were washed-out from phosphate binders at the baseline, their median serum levels of phosphate, PTH and alkaline phosphatase were above upper limit. As expected, bone turnover markers such as alkaline phosphatase and deoxypyridinoline were also slightly elevated (Table 1).

3.2. Baseline bone histomorphometry

Bone biopsies were classified according to the TMV system. Overall, 28 patients (54.9%), 23 (45.1%) and only one patient (2%) exhibited low, high, and normal bone turnover, respectively. Half of the patients had low bone volume and mineralization was impaired in 28 patients (53.8%). Ct.Po was above normal range in 44 patients (85%), with a diffuse pattern, as exemplified in Fig. 2. At baseline, the mean Ct.Po was not different regarding race ($p = 0.24$), gender ($p = 0.12$) and TMV status.

Ct.Po at baseline correlated with PTH ($r = 0.432$; $p = 0.001$), cortical thickness ($r = 0.542$, $p < 0.0001$, as shown in Fig. 3A and B, respectively. Ct.Po had a tendency toward a correlation with bone alkaline phosphatase ($r = 0.249$; $p = 0.078$) and fibrosis ($r = 0.243$, $p = 0.08$).

3.3. Follow-up data

Out of 52 patients, 21 received calcium acetate and 31 received sevelamer hydrochloride. In an attempt to increase or decrease bone turnover based on baseline bone biopsy, among the 23 patients with high turnover, 14 remained high turnover and 9 turned into low. In addition, among the 28 patients with low turnover, 16 remained low and 12 turned into high turnover.

As shown in Table 1, after one-year treatment, the median of serum phosphate and 25-vitamin D decreased, whereas ionized calcium increased. Overall, PTH levels increased, although non-significantly. However, this result was seen only among those with low turnover status [from 189.5 pg/ml (57–451) to 300 pg/ml (118–632); $p = 0.03$], while non-significant change occurred among those with high turnover [from 584 pg/ml (218–1002) to 433 pg/ml (278–842); $p = 0.73$]. The delta of PTH correlated with the delta of bone formation rate ($r = 0.28$; $p = 0.04$).

3.4. Ct.Po analysis after one-year treatment

Ct.Po increased in 32 patients and decreased in 20 patients. Overall, the median Ct.Po increased, reaching abnormally high values after one-year treatment in 49 (94%) patients. The delta of Ct.Po correlated with the delta of cortical thickness ($r = 0.65$, $p < 0.03$), the delta of phosphate ($r = 0.337$, $p = 0.015$; Fig. 3C), the delta of PTH, as absolute and percentage values ($r = 0.295$, $p = 0.04$; Fig. 3D and $r = 0.297$; $p = 0.03$, respectively), and had a tendency to correlate with the delta of DPD ($r = 0.265$, $p = 0.06$). The delta of Ct.Po did not correlate with the delta of BV/TV or the mineralization parameters. After one-year treatment Ct.Po was higher in non-white than in white patients (46 ± 19% in vs. 35% ± 17%, respectively; $p = 0.039$). The delta of Ct.Po from baseline to one year after was significant only in non-white patients ($p = 0.0037$), as shown in Fig. 4. The risk of having an increase in delta of Ct.Po was 4.5 times higher in non-white than in white patients. There were no differences in the delta of Ct.Po regarding trabecular bone turnover ($p = 0.82$). Indeed, Ct.Po increased an average 8.0 patients who went from high to low turnover against 9.1% in those who did not change bone turnover ($p = 0.906$). Delta of Ct.Po was also not influenced by gender ($p = 0.95$), use of sevelamer vs. calcium as a phosphate binder ($p = 0.25$), calcitriol use ($p = 0.24$) and dialysate calcium concentration ($p = 0.23$). Multiple regression analysis showed that the delta of Ct.Po was dependent on delta of PTH ($p = 0.006$) and race ($p = 0.006$), in a model adjusted for age, gender, therapy, delta of phosphate, and delta of deoxypyridinoline ($r^2 = 0.215$).

4. Discussion

The BRIC study, which led to the current analysis, randomized CKD patients to receive either sevelamer or calcium acetate as a phosphate binder. The one-year treatment was based on bone biopsy findings and has focused on trabecular bone turnover improvement, despite serum PTH changes. We analyzed cortical compartment in a subset of these patients, demonstrating the following: first, Ct.Po was already high at baseline in the majority of patients and correlated with PTH levels, despite turnover status. Second, PTH rose in patients with low bone turnover, as intended, which correlated with bone formation rate. Third, neither gender nor any choice of clinical treatment has affected Ct.Po increase. Finally, Ct.Po increased after one-year treatment in the majority of patients, although this increase was striking only in non-white patients.

The association between cortical architecture impairment and fractures is well documented in osteoporosis, mainly in postmenopausal women [11,12]. There are ex-vivo studies on iliac crest bone biopsies that showed alterations of both trabecular and cortical microarchitecture in subjects with fractures [13]. Qiu et al. have showed that a deficit in cortical bone had similar effects as a deficit in cancellous bone concerning an increase in the risk of fracture. In addition, the authors demonstrated that in individuals with both cortical and cancellous bone deficit, the likelihood of fracture was much higher than in patients with deficits in either cortical or cancellous bone alone [14]. In respect to CKD patients, descriptions of the cortical compartment are scarce, showing high prevalence of cortical abnormalities, with elevated Ct.Po in >50% of patients on hemodialysis [15]. Furthermore, in agreement with our data, Malluche et al. have demonstrated that Ct.Po was higher

Table 1
Biochemical and cortical bone parameters at baseline and after one year.

	Baseline	One year	Delta	p	Reference values
P (mg/dl)	6.7 (6.3, 7.7)	5.5 (4.7, 6.6)	−1.4 (−2.1, −0.7)	<0.0001	2.7–4.5
iCa (mmol/l)	1.25 (1.20, 1.31)	1.29 (1.25, 1.38)	0.07 (0, 0.12)	<0.0001	4.6–5.3
AP (U/l)	202 (160, 282)	190 (130, 289)	−19 (−73, 66)	0.314	40–129 (men) 35–104 (women)
PTH (pg/ml)	265 (124, 633)	372 (178, 639)	48 (−56, 194)	0.183	15–65
DPD (nmol/l)	74 (47, 113)	89 (38, 190)	7 (−11, 85)	0.142	3.25 ± 0.66
BAP (U/l)	24 (16, 31)	28 (16, 34)	3 (−7, 14)	0.437	11.6–42.7
25OHvitD (ng/ml)	33 (19, 42)	25 (18, 33)	−4 (−14, 2)	0.003	18–62
Ct.Po, %	29.3 (17.9, 45.8)	35.5 (26.6, 53.4)	6.5 (−1, 23.5)	0.030	1.9–10

Data expressed as mean ± SD or median (25, 75).
P = phosphorus; iCa = ionized calcium; AP = alkaline phosphatase; PTH = parathormone; DPD = deoxypyridinoline; BAP = bone alkaline phosphatase; 25OHvitD = 25-hidroxivitaminD; Ct.Po = cortical porosity.

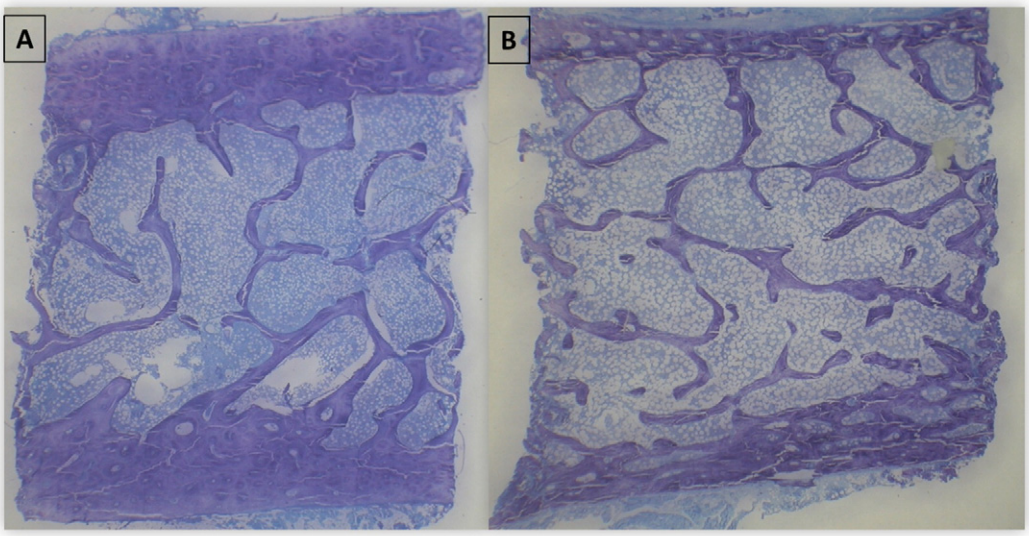

Fig. 2. Comparison of cortical compartments in bone biopsies. A. Bone biopsy with normal cortical thickness and cortical porosity from a non-CKD patient. B. Bone biopsy with high porosity and low cortical thickness from a dialysis patient. Toluidine blue staining (×16).

in non-white CKD patients as compared to white CKD patients [3]. Moreover, bone trabecular compartment is usually evaluated through the TMV classification and used to guide treatment [10]. However, changes in this compartment do not reflect changes in the cortical compartment. We demonstrated that an increase in Ct.Po was not accompanied by a decrease in bone trabecular volume. Therefore, our data suggests that cortical compartment should be included in the volume criteria of the TMV classification.

Cortical bone is more adversely affected than trabecular bone in hyperparathyroidism [16]. Elevated PTH levels are catabolic for cortical bone and this biochemical alteration could cause deterioration in cortical architecture, leading to reduced cortical density and increased Ct.Po.

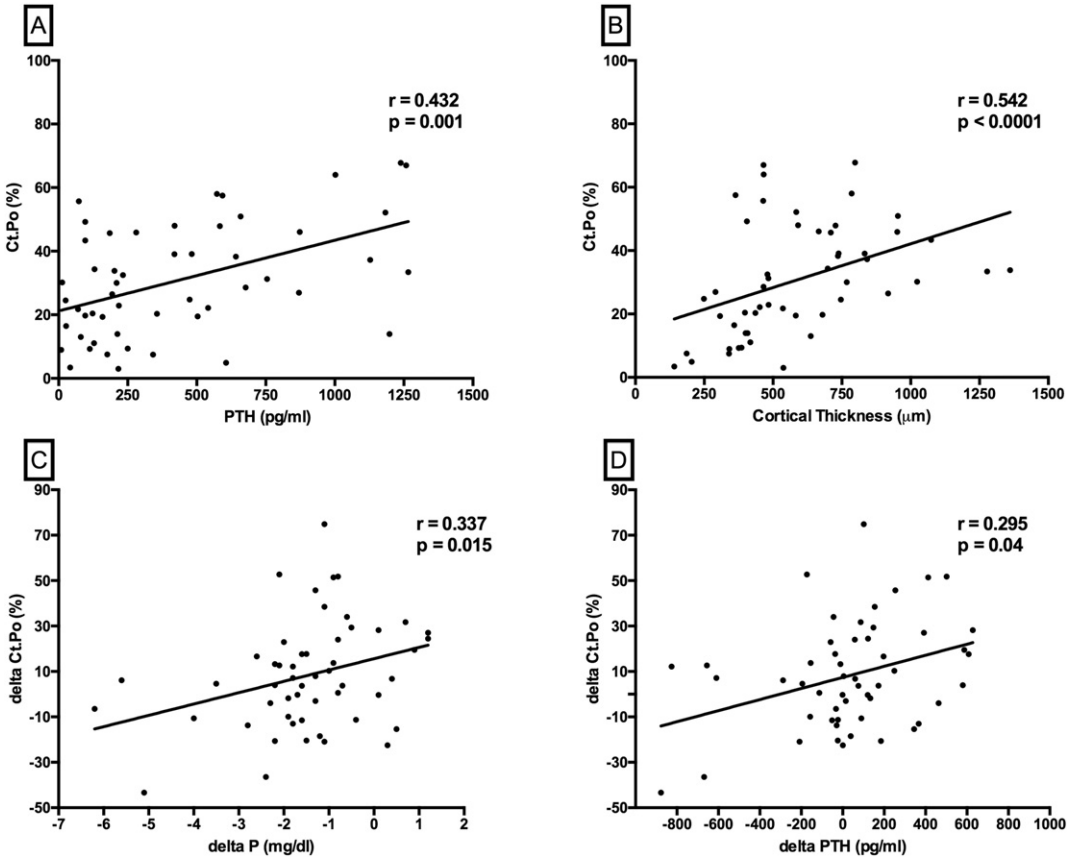

Fig. 3. Correlations between Cortical Porosity at Baseline and after one-year treatment. A. Relationship between cortical porosity (Ct.Po) and parathyroid hormone (PTH), both measured at baseline. B. Relationship between cortical porosity (Ct.Po) and cortical thickness, both measured at baseline. C. Relationship between the delta of cortical porosity (Ct.Po) and the delta of phosphate (P). D. Relationship between the delta of cortical porosity (Ct.Po) and the delta of parathyroid hormone (PTH). Delta: change from baseline to one year later.

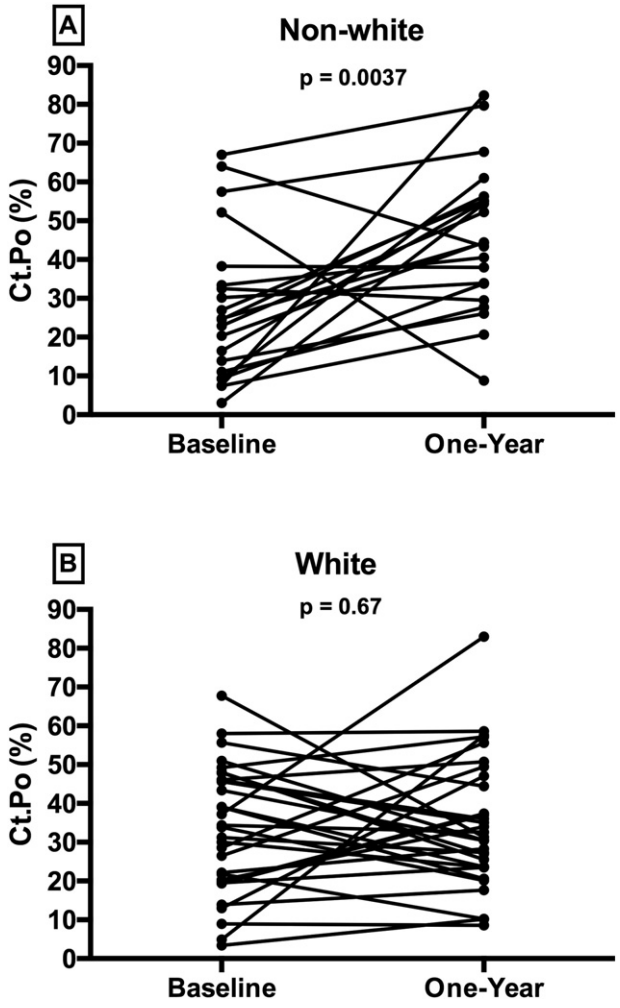

Fig. 4. A before and after plot of the cortical porosity (Ct.Po) according to race, in non-white (panel A) and white patients (panel B). Pre and post Ct.Po refereed to baseline and one-year after measurement.

This happens in the course of CKD much earlier than previously thought [1]. In our patients, we have observed higher levels of PTH among those with higher Ct.Po. Moreover, the increase in PTH levels over time enhanced the progression of Ct.Po. Of note, chronic excess of PTH secretion is catabolic for cortical bone, causing marked subperiosteal and intracortical erosion. In contrast, chronic excess of PTH may also cause increased osteoblastic bone formation benefiting the periosteum, which in turn may compensate for the loss of cortical bone to some extent, as well as increased trabecular thickness and number [17]. Confirming those preclinical findings, a histomorphometric study in primary hyperparathyroidism demonstrated that PTH preferentially affects cortical bone, resulting in periosteal resorption and intracortical porosity [18]. As hyperphosphatemia is a common finding among patients with secondary hyperparathyroidism, one can argue that phosphate instead of PTH has an effect on cortical porosity. Indeed, our group has shown in a previous experimental study that phosphate had a PTH-independent effect on bone trabecular volume [19]. Although we found a correlation between delta of phosphate and the delta of Ct.Po, it was a weak correlation, which did not remain significant in the multivariate analysis. As in a clinical scenario it is virtually impossible to evaluate the isolated effect of either PTH or phosphate, further studies are necessary to clarify this mechanism.

Studies applying high-resolution peripheral quantitative computed tomography in CKD patients have shown a selective decrease in cortical measures caused by elevated levels of PTH, which was demonstrated by Jamal et al. in patients older than 50 years, on hemodialysis. It was found that cortical thickness was strongly associated with fractures and inversely correlated with PTH [20]. Studies on CKD patients not on dialysis also demonstrated that a decrease in cortical area and thickness were associated with an increase fracture risk [21,22], and the cortical measures were even more associated with fractures as compared with trabecular measures [21].

There are few studies on the effects of CKD-MBD clinical treatment on the cortical compartment. Moe et al., using a rat model of CKD with secondary hyperparathyroidism, have compared the efficacy of treatment with zoledronic acid and calcium used as a phosphate binder. Ct.Po increased in CKD animals when compared to normal animals, with significant reduction in those treated with calcium plus zoledronic acid. Lowering PTH was more effective in improving Ct.Po and biomechanical integrity. They concluded that based on the strong correlation between PTH, but not calcium, with Ct.Po, the efficacy of calcium on bone was more likely PTH-mediated [16]. A Japanese group reported a case of a patient with ABD treated with lanthanum carbonate for 10 months, and had a bone biopsy showing a decrease in Ct.Po from 12,6% to 2,1%, while PTH decreased from 42 to 31 pg/ml [23]. Last, Ishimura et al. [24] showed that cortical bone, rather than cancellous bone, was particularly affected by cinacalcet treatment, a therapy to suppress PTH. Taken together, the above-described data suggest that decrease in PTH could be helpful for improving cortical integrity. Corroborating with this belief, our data shows that with an increase of PTH, the Ct.Po increases over time. Of note, even patients that were receiving calcium carbonate had a reduction in dialysate calcium concentration, as well as in calcitriol dose. However, as none of the previous studies included CKD patients on hemodialysis, our findings have significant clinical implications, while demonstrating that Ct.Po should be considered while treating these patients.

Our study has some limitations. First, it is a post-hoc analysis of a study in which cortical evaluation was not a primary end-point. Of note, we have evaluated nearly 50% of this initial population, based on the CtPo measurement availability. Secondly, doses of phosphate binders and analogs of vitamin D were not assessed. Finally, while it demonstrates significant increase in Ct.Po in association with an increase of PTH levels, it does not demonstrate a cause-effect relationship with fracture because there was no long-term follow-up. In addition, the clinical relevance of higher Ct.Po is not well established. Cortical compartment is implicated in a higher risk of fracture and is overlooked in patients on hemodialysis. The clinical treatment of CKD-MBD does not focus on this compartment and bone biopsy is not always available for these patients. In this respect, our findings have significant clinical implications: converting low to high bone turnover may be associated with an increase of cortical porosity. Whether this finding leads to a high risk of fracture deserves further investigation.

In summary, we have reported novel data demonstrating that CKD patients on hemodialysis, regardless of clinical therapy choice, have a high Ct.Po. In an attempt to increase bone turnover, the increase in PTH levels might be associated with higher cortical porosity, mainly in non-white patients.

Funding

There is no funding.

Conflict of interest

Rosa M. A. Moysés, Maria E. Canziani, Aluizio B. Carvalho and Vanda Jorgetti have received research grants from Sanofi and were consultants to Sanofi, Abbott, and Amgen. All other authors state they have no conflict of interest.

Authors' role

Study design: MJCLNA, CK, RME, MEC, ABC, VJ, RMAM; Study conduct: MJCLNA, CK, FCB; DVB, RMAM; Data analysis: MJCLNA, CK, RME, RMAM; Data interpretation: MJCLNA, RME, RMAM; Drafting manuscript: MJCLNA, RME, RMAM; Approving final version of manuscript: MJCLNA, CK, RME, FCB; DVB, MEC, ABC, VJ, RMAM. RMAM takes responsibility for the integrity of the data analysis.

Acknowledgments

Rosa M. A. Moysés, Maria E. Canziani and Vanda Jorgetti are supported by CNPQ (Conselho Nacional de Desenvolvimento Científico e Tecnológico) (304249/2013-0). This study was presented, in part, at the ASN Kidney Week, Philadelphia, USA in 2014.

References

[1] T.L. Nickolas, M.B. Leonard, E. Shane, Chronic kidney disease and bone fracture: a growing concern, Kidney Int. 74 (2008) 721–731.
[2] T.L. Nickolas, S. Cremers, A. Zhang, V. Thomas, E. Stein, A. Cohen, R. Chauncey, L. Nikkel, M.T. Yin, X.S. Liu, S. Boutroy, R.B. Staron, M.B. Leonard, D.J. McMahon, E. Dworakowski, E. Shane, Discriminants of prevalent fractures in chronic kidney disease, J. Am. Soc. Nephrol. 22 (2011) 1560–1572.
[3] H.H. Malluche, H.W. Mawad, M.C. Monier-Faugere, Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients, J. Bone Miner. Res. 26 (2011) 1368–1376.
[4] T.L. Nickolas, E.M. Stein, E. Dworakowski, K.K. Nishiyama, M. Komandah-Kosseh, C.A. Zhang, D.J. McMahon, X.S. Liu, S. Boutroy, S. Cremers, E. Shane, Rapid cortical bone loss in patients with chronic kidney disease, J. Bone Miner. Res. 28 (2013) 1811–1820.
[5] D.V. Barreto, F.C. Barreto, A.B. de Carvalho, L. Cuppari, S.A. Draibe, M.A. Dalboni, R.M. Moyses, K.R. Neves, V. Jorgetti, M. Miname, R.D. Santos, M.E. Canziani, Phosphate binder impact on bone remodeling and coronary calcification—results from the BRiC study, Nephron Clin Pract 110 (2008) c273–c283.
[6] J.D. Hernandez, K. Wesseling, R. Pereira, B. Gales, R. Harrison, I.B. Salusky, Technical approach to iliac crest biopsy, Clin. J. Am. Soc. Nephrol. 3 (Suppl. 3) (2008) S164–S169.
[7] A.M. Parfitt, M.K. Drezner, F.H. Glorieux, J.A. Kanis, H. Malluche, P.J. Meunier, S.M. Ott, R.R. Recker, Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee, J. Bone Miner. Res. 2 (1987) 595–610.
[8] L.M. Dos Reis, J.R. Batalha, D.R. Muñoz, A. Borelli, P.H. Correa, A.B. Carvalho, V. Jorgetti, Brazilian normal static bone histomorphometry: effects of age, sex, and race, J. Bone Miner. Metab. 25 (2007) 400–406.
[9] S. Vedi, J.E. Compston, A. Webb, J.R. Tighe, Histomorphometric analysis of dynamic parameters of trabecular bone formation in the iliac crest of normal British subjects, Metab Bone Dis Relat Res 5 (1983) 69–74.
[10] Kidney Disease: Improving Global Outcomes CKDMBDWG. 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) S1–130.
[11] E. Sornay-Rendu, S. Boutroy, F. Munoz, P.D. Delmas, Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY study, J. Bone Miner. Res. 22 (2007) 425–433.
[12] E. Sornay-Rendu, J.L. Cabrera-Bravo, S. Boutroy, F. Munoz, P.D. Delmas, Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women, J. Bone Miner. Res. 24 (2009) 737–743.
[13] E. Sornay-Rendu, S. Boutroy, F. Munoz, M.L. Bouxsein, Cortical and trabecular architecture are altered in postmenopausal women with fractures, Osteoporos. Int. 20 (2009) 1291–1297.
[14] S. Qiu, D.S. Rao, S. Palnitkar, A.M. Parfitt, Independent and combined contributions of cancellous and cortical bone deficits to vertebral fracture risk in postmenopausal women, J. Bone Miner. Res. 21 (2006) 1791–1796.
[15] T. Adragao, J. Herberth, M.C. Monier-Faugere, A.J. Branscum, A. Ferreira, J.M. Frazao, H.H. Malluche, Femoral bone mineral density reflects histologically determined cortical bone volume in hemodialysis patients, Osteoporos. Int. 21 (2010) 619–625.
[16] S.M. Moe, N.X. Chen, C.L. Newman, V.H. Gattone, J.M. Organ, X. Chen, M.R. Allen, A comparison of calcium to zoledronic acid for improvement of cortical bone in an animal model of CKD, J. Bone Miner. Res. 29 (2014) 902–910.
[17] M.A. Miller, J. Chin, S.C. Miller, J. Fox, Disparate effects of mild, moderate, and severe secondary hyperparathyroidism on cancellous and cortical bone in rats with chronic renal insufficiency, Bone 23 (1998) 257–266.
[18] Y. Duan, V. De Luca, E. Seeman, Parathyroid hormone deficiency and excess: similar effects on trabecular bone but differing effects on cortical bone, J. Clin. Endocrinol. Metab. 84 (1999) 718–722.
[19] K.R. Neves, F.G. Graciolli, L.M. dos Reis, C.A. Pasqualucci, R.M. Moyses, V. Jorgetti, Adverse effects of hyperphosphatemia on myocardial hypertrophy, renal function, and bone in rats with renal failure, Kidney Int. 66 (2004) 2237–2244.
[20] S.A. Jamal, J. Gilbert, C. Gordon, D.C. Bauer, Cortical pQCT measures are associated with fractures in dialysis patients, J. Bone Miner. Res. 21 (2006) 543–548.
[21] S. Jamal, A.M. Cheung, S. West, C. Lok, Bone mineral density by DXA and HR pQCT can discriminate fracture status in men and women with stages 3 to 5 chronic kidney disease, Osteoporos. Int. 23 (2012) 2805–2813.
[22] T.L. Nickolas, E. Stein, A. Cohen, V. Thomas, R.B. Staron, D.J. McMahon, M.B. Leonard, E. Shane, Bone mass and microarchitecture in CKD patients with fracture, J. Am. Soc. Nephrol. 21 (2010) 1371–1380.
[23] A. Yajima, M. Inaba, Y. Tominaga, M. Tanaka, S. Otsubo, K. Nitta, A. Ito, S. Satoh, Impact of lanthanum carbonate on cortical bone in dialysis patients with adynamic bone disease, Ther. Apher. Dial. 17 (Suppl. 1) (2013) 41–48.
[24] E. Ishimura, S. Okuno, N. Tsuboniwa, M. Ichii, K. Yamakawa, T. Yamakawa, S. Shoji, Y. Nishizawa, M. Inaba, Effect of cinacalcet on bone mineral density of the radius in hemodialysis patients with secondary hyperparathyroidism, Clin. Nephrol. 76 (2011) 259–265.