Low Turnover Bone Disease in Early CKD Stages

To the Editor: We read with interest the article "Low Turnover Renal Osteodystrophy With Abnormal Bone Quality and Vascular Calcification in Patients With Mild-to-Moderate CKD" by El-Husseini *et al.*[1] On the basis of bone biopsy findings, the authors reported that low turnover bone (LTB) disease was the most prevalent pattern of renal osteodystrophy in patients with early CKD stages 2 to 3, with a prevalence of 84%. This finding is in agreement with previous reports by Coen *et al.*[2] (not mentioned) and ourselves.[3] Both reports included a larger number of predialysis patients with CKD, and we were the first a few years ago to report the predominance of LTB disease in CKD stages 2 to 3. Moreover, we would like to take issue with the authors' statement in the Discussion that Neto *et al.*[4] found a high percentage of normal bone histology in patients with CKD stages 3 to 4. They actually also reported that LTB disease was the predominant form of renal osteodystrophy in these patients. Taken together, we are pleased that El-Husseini *et al.*[1] confirm these previous reports.

Of note, Barreto *et al.*[3] reported that bone formation rate was lower in patients with CKD stages 2 to 3, as compared with patients with CKD stages 4 to 5, which may in part be due to the skeletal action of uremic toxins, inducing a resistance to the action of parathyroid hormone.[2] Together with the report by Coen *et al.*,[2] these observations led us to postulate that the bone disease pattern in CKD changes along the decline in kidney function, switching from LTB in early stages to high bone turnover in more advanced stages of CKD.[5] Excessive parathyroid hormone lowering at CKD stages 2 to 3 should be avoided because this may aggravate LTB.[5]

Finally, El-Husseini *et al.*[1] claim that Fourier transform infrared spectroscopy has added value in evaluating bone quality in LTB disease. We wonder whether the assessment of bone mineral-to-matrix ratio by infrared spectroscopy allows an accurate evaluation of bone quality and strength as bone histomorphometry in patients with CKD with LTB disease. Moreover, we question the applicability of infrared spectroscopy in clinical practice.

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2. Coen G, Mazzaferro S, Ballanti P, et al. Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross sectional study. *Nephrol Dial Transplant.* 1996;11:813–819. https://doi.org/10.1093/oxfordjournals.ndt.a027404
3. Barreto FC, Barreto DV, Canziani ME, et al. Association between indoxyl sulfate and bone histomorphometry in predialysis chronic kidney disease patients. *J Bras Nefrol.* 2014;36:289–296. https://doi.org/10.5935/0101-2800.20140042
4. Neto R, Pereira L, Magalhães J, et al. Sclerostin and DKK1 circulating levels associate with low bone turnover in patients with chronic kidney disease stages 3 and 4. *Clin Kidney J.* 2021;14:2401–2408. https://doi.org/10.1093/ckj/sfab081
5. Drüeke TB, Massy ZA. Changing bone patterns with progression of chronic kidney disease. *Kidney Int.* 2016;89:289–302. https://doi.org/10.1016/j.kint.2015.12.004

Fellype Carvalho Barreto[1], Ziad A. Massy[2,3] and Tilman B. Drueke[3]

[1]Division of Nephrology, Department of Internal Medicine, Federal University of Paraná, Curitiba, Paraná, Brazil; [2]Division of Nephrology, Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris, Boulogne Billancourt, Paris, France; and [3]Institut National de la Santé et de la Recherche Médicale U-1018, Team 5, Centre de Recherche en Epidémiologie et Santé des Populations, Versailles Saint-Quentin-en-Yvelines University (Paris-Ile-de-France-Ouest University), Paris-Sud University and Paris Saclay University, Villejuif, France

Correspondence: Fellype Carvalho Barreto, Division of Nephrology, Department of Internal Medicine, Federal University of Paraná, Rua General Carneiro, 25, Curitiba, Paraná 80060-900, Brazil. E-mail: fellype.barreto@ufpr.br

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Response to "Low Turnover Bone Disease in Early CKD Stages"

The Authors Reply: Barreto *et al.* wrote a letter titled, "Low Turnover Bone Disease in Early CKD Stages" in response to our manuscript, "Low Turnover Renal Osteodystrophy With Abnormal Bone Quality

and Vascular Calcification in Patients With Mild-to-Moderate CKD.''

Our results confirm prior reports (including that of Barreto *et al*.) of lower bone turnover at milder reductions of glomerular filtration rate compared with more progressed loss of kidney function. However, the report by Barreto *et al*.[1] reveals histomorphometric data with high osteoclastic surface that is not fully supportive of the diagnosis of low bone turnover. Furthermore, the finding of very high mineralization lag times requires explanation. The same patients were first reported by Tomiyama *et al*.[2] They were selected for various reasons, including cardiovascular disease. This raises the question of immobilization influencing histomorphometric results.

We have carefully ruled out patients with any abnormalities known to affect bone turnover to ensure that changes observed are only related to reduced kidney function. We had more Whites and older patients than Barreto *et al*.[1]

The 1996 article by Coen *et al*.[3] found only 9 of 76 patients with chronic kidney disease with adynamic bone disease at a creatinine clearance of 19.5 $\pm$ 11.9 ml/min. Patient selection criteria were not given. Neto *et al*.[4] found more patients in the normal bone histology group than in any other.

Thus, our patient population is different from those studied in prior publications. We have cited the more recent publications. Confirming prior publications is important and aids in the acceptance of the data by the scientific and clinical community.

Fourier-transform infrared spectroscopy has not been done before on bone samples from this patient population. We did not intend to present Fourier-transform infrared spectroscopy as a routine clinical diagnostic tool. We agree that currently it is mainly a research method, but it adds valuable information on bone quality which cannot be obtained by histomorphometry. The measured mineral-to-matrix ratio is a key parameter of bone composition and has been found to be related to bone stiffness and energy to fracture. Our manuscript provided references for further information on this novel tool for assessment of bone quality.

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Amr El-Husseini[1], Mohamed Abdalbary[1], Florence Lima[1], Daniel Davenport[2], Marie-Claude Faugere[1] and Hartmut H. Malluche[1]

[1]Division of Nephrology, Bone and Mineral Metabolism, University of Kentucky, Lexington, Kentucky, USA and [2]Division of Healthcare Outcomes & Optimal Patient Services, University of Kentucky, Lexington, Kentucky, USA

Correspondence: Hartmut H. Malluche, Division of Nephrology, Bone & Mineral Metabolism, University of Kentucky Chandler Medical Center, 800 Rose Street, MN-564, Lexington, Kentucky 40536-2637, USA. E-mail: hhmall@uky.edu

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