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Epidemiology of Renal Osteodystrophy in R. Macedonia

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Introduction

Chronic renal failure (CRF) has a repercussion on bone, known as renal osteodystrophy (ROD), even before dialysis treatment is started (1). To date, the gold standard for diagnosis of ROD remains histomorphometric and histochemical examination of a bone biopsy specimen (2). Five types of bone disease can be distingueshed: osteomalacia (OM), adynamic bone disease (ABD), hyperparathyroid bone disease (HPTH), mixed lesion (Mx) and normal bone (N). In recent years, an evolution in the spectrum of renal osteodystrophy (ROD) in renal failure patients has been noticed with ABD as most prevalent type of bone disease (3). Various biochemical markers have been frequently evaluated over the last decades, as an alternative of the invasive bone biopsy method. With regard to the letter, most investigators measure intact parathyroid hormone (iPTH), total or ionized serum calcium (Ca), phosphate (P), alkaline phosphatase (AP), vitamin D status and some markers of either bone formation [bone alkaline phosphatase (BAP), osteocalcin (OC)] or bone resorption [(deoxy-) pyridinolines (DPYD, PYD)]. However, these markers do not always reach a high enough diagnostic performance to substitute for bone histomorphometry (4). The management of ROD patients undergoing dialysis have experimented great changes, but they have not been uniform in all countries. Hence, the diagnosis and treatment guidelines have not yet been standardized. So far, ROD continues to be a dilemma for daily clinical practice (5). In this paper we report the current measures in prevention, biochemical diagnosis and treatment of ROD in dialysis patients in R. Macedonia.

Methods

At the beginning of 2005, all 18 HD Centers in our country were invited to fill in a questionnaire, with data related to the problem of ROD. A total of 16 Centers (88.8%) replied on this epidemiological survey including the data from 588 patients. The first part of the questionnaire was related to the clinical data (age, gender, renal diagnosis, duration of hemodialysis). The second set of data focused on the last determination of serum biochemical parameters: calcium (Ca), phosphate (P), total alkaline phosphatase (TAP), parathyroid hormone (PTH), osteocalcin (OC). Finally, the last set of data tried to identify the current therapeutical practice for dialysate Ca concentration, phosphate binding, vitamin D treatment and performed parathyroidectomy (PTx). The questionnaire was sent together with a letter explaining the goals of the study and here we provide a preliminary and descriptive analysis of the main results.

Results

The provided information on 588 patients represents 57.3% of our hemodialysis population. The demographic characteristics were mean age of 53.3y, range (17-84), mean dialysis duration of 6.8±6.1y and 62.4% males being at similar age, renal diagnosis and dialysis duration as females.

The number of patients with mean serum Ca concentration being within recommended levels established by the National Kidney Foundation (2.1–2.4 mM) was found to be as much as 40%. Serum Ca below this level (<2.1 mM) was found in 19.9% and 40.1% of the patients were assessed to be at level above 2.4 mM. An ideal serum phosphate control (<1.8 mM) was achieved in 67% and Ca x P product <4.4 was calculated in 71.1% of the patients.

The desired level of PTH was considered to be between 150 and 250 pg/ml and it was achieved in only 13.6% of patients. A relatively small proportion of patients (12.5%) were found within the interval between 250 and 450 pg/ml. PTH above 450 pg/ml, considered as hyperparathyroid bone disease, was found in 31.1% of the patients. Still, the largest part of patients presented with PTH below 150 pg/ml, which was considered as adynamic bone disease and calculated in 42.8% of the patients. This relatively inactive state of bone formation was also confirmed with findings of OC < 23 ng/ml (high performance for diagnosis of ABD) in 63.6% of the study population. Conversely, TAP level <45 U/L was found only in 4.4% of the patients, which might be explained by the high percentage of HCV positivity (46.9%) as a confounding factor.

The cases with severe HPTH and an indication for parathyroidectomy were referred in only 7% of patients. The low dialysate Ca concentration of 1.25 mM was used in only 6.1% of the dialysis population. Calcium carbonate was the most widely administered phosphate binding agent in 95.6% of patients, with a relatively small dose between 0.5 and 3 gr/day used in 72.1% of the patients. Vitamin D (1-2 μg/week) was prescribed in almost half of the patients (47.4%).

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Discussion

Renal osteodystrophy, in which abnormalities of bone turnover predominate, continues to be a complication of CRF patients and is associated with morbidity and poor quality of life. The concept of ROD is more than 50 years old but has undergone many changes and a great evolution, especially in the last three decades (3). While in the 1970s the imperative was prevention of development of HPTH with improving the control of hyperphosphatemia, in 1980s the attention was paid on preventive measures of the consequences of aluminum treatment. At the end of the 1980s and beginning of the 1990s vitamin D's active metabolites and calcium phosphate binders become a current therapy for the management of secondary hyperparathyrodisim. It was recently shown that the over-suppression of PTH and ABD as predominant type of ROD contribute to high levels of calcium and phosphorus in the blood, which are strongly associated with cardiovascular disease, a major cause of mortality and morbidity (6). Hence, there was a need for an alternative phosphate binder that is not associated with these known side effects during phosphate control. Lately, sevelamer hydrochloride (Renagel®) and lanthanum carbonate (Fosrenol®) become available on the market as non-aluminum, non-calcium based phosphate binders which are well-tolerated and effectively reduces serum phosphorus levels (7,8).

As a result of aforementioned evolution of rod and the important geographic variations (1,9), present study assessed the distribution of ROD through the diagnosis of the current bone marker status and defined the appropriate therapeutic targets.

The substantial proportion of the patients in present study presented with low bone formation markers (PTH, OC). Hence, ABD was assumed as predominant bone disease in our population (42.8%), confirming the previous reports (10). This is in line with the observation that more than 40% of the patients presented with sustained hypercalcemia (serum Ca levels above 2.4 mM), implying a higher risk of extra-osseous calcifications. However, the Ca x P product was under the proposed limit of 4.4 in more than 70% of the patients, meaning a good phosphate control has been achieved.

Therapeutically, the very small proportion of patients using low Ca dialysate (6%) should be taken into consideration as an imperative in the medical treatment for this ABD population. Furthermore, non-aluminum, non-calcium based phosphate binders should be administered whenever it is possible and vitamin D treatment be restricted to a few cases with severe HPTH. All of these measures should promote an increase in the bone formation rate and improve the buffer capacity of the bone for handling of calcium influx, thus preventing extraskeletal and cardiovascular calcifications and the patients' morbidity.

Conclusion

In conclusion, this analysis gives useful information for the existing gap between diagnosis and treatment of ROD in our country. The use of high (1.75 mM) dialysate Ca concentration, calcium carbonate and vitamin D treatment might be associated with development of ABD.

Key words: dialysis, bone markers, renal osteodystrophy, adynamic bone disease.

Reference

1. Spasovski G, Bervoets A, Behets G, Ivanovski N, Sikole A, Dams G, Couttenye MM, De Broe ME, D'Haese PC. Spectrum of renal bone disease in end-stage renal failure patients not in dialysis yet. *Nephrol Dial Transplant* 2003; 18:1159-1166.
2. Spasovski GB: Bone biopsy as a diagnostic tool in the assessment of renal osteodystrophy. *The Int J Artif Organs* 2004; 27(11):918-923.
3. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, Saiphoo C, Fenton SS, Segre GV. The spectrum of bone disease in end-stage renal failure. An evolving disorder. *Kidney Int* 43:436-442, 1993
4. Bervoets ARJ, Spasovski G, Behets GJ, Dams G, Polenakovic MH, Zafirovska K, Van Hoof VO, De Broe ME and D'Haese PC. Useful biochemical markers for diagnosing renal osteodystrophy in predialysis end-stage renal failure patients. *Am J Kidney Dis* 2003; 41:997-1007.
5. Malluche H, Faugere MC. Renal bone disease 1990: an unmet challenge for the nephrologist. *Kidney Int* 38:193-211, 1990
6. Goodman WG, Goldin J, Kuizon BD: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342:1478-1483.
7. Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, Bonventre JV, Slatopolsky E: Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 29:66-71, 1997
8. D'Haese PC, Spasovski G, Sikole A, Hutchison A, Freemont TJ, Sulkova S, Swanepoel C, Pejanovic S, Djukanovic L, Balducci A, Coen G, Sulowicz W, Ferreira A, Torres A, Curic S, Popovic M, Dimkovic N and De Broe ME. Multi-Centre Study on the Effects of Lanthanum Carbonate (Fosrenol®) and Calcium Carbonate on Renal Bone Disease in Dialysis Patients. *Kidney Int* 63:S73-78, 2003.
9. Diaz Lopez JB, Jorgetti V, Caorsi H, *et al*. Epidemiology of renal osteodystrophy in Iberoamerica. *Nephrol Dial Transplant 1998*; 13(Suppl 3):41-45.
10. Couttenye MM, D'Haese PC, Van Hoof VO, Lemoniatou E, Goodman W, Verpooten GA and De Broe ME. Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in hemodialysis patients. *Nephrol Dial Transplant* 1996; 11:1065-1072.