Strategies to manage low-bone turnover

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ABSTRACT

A change in paradigm occurred lately whereby not hypocalcemia but hypercalcemia and positive calcium balance were considered negative factors. Namely, the use of calcium-based binders in combination with vitamin D analogues, has been shown to lead to an over-suppression of parathyroid hormone (PTH) and development of low-bone turnover adynamic bone disease (ABD). The changing prevalence of various types of bone diseases from a high to low-bone turnover goes in line with the presence of increased risk for vascular calcification (VC), morbidity and mortality in the dialysis population. The attenuation of the previous great expectations in calcium-based phosphate binders and vitamin D-analogues entailed a new treatment strategy to preserve bone and vascular health. Hence, a new evidence for treatment of ABD with various types of non calcium based binders and low calcium dialysate is presented. Sevelamer treatment has reduced calcium concentration and increased PTH levels, resulting in the improvement of markers of bone turnover, increased bone formation and improved trabecular architecture, providing a slower progression of VC. Data on lanthanum beneficial effect on ABD histology have been demonstrated in long-term clinical studies. Although there is a slow release of lanthanum from its bone deposits after discontinuation of the treatment and no association with aluminium-like bone toxicity, there is still an ongoing scientific debate about its long-term toxic potential. Finally, reducing the number of calcium based binders and low calcium dialysate (1.25 mmol/l) has been reported to have an impact on the evolution towards markers reflecting higher bone turnover. Then, adoption of the non calcium-based binders should be reserved to high risk patients with ABD and progression of vascular calcifications associated with increased morbidity and mortality.

Key words: Adynamic bone disease. Calcium based phosphate binders. Low calcium dialysate. Non-calcium based phosphate binders

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RESUMEN

Recientemente se ha cambiado de parecer en cuanto al paradigma por el que la hipercalcemia, en lugar de la hipocalcemia, y el equilibrio positivo de calcio se consideraban factores negativos. En otras palabras, se ha demostrado que el uso de quelantes cálcicos junto con análogos de vitamina D conlleva una sobresupresión de la hormona paratiroidea (PTH) y la aparición de enfermedad ósea adinámica (EOA) o de bajo remodelado (EOBR). La prevalencia variable de los diferentes tipos de enfermedades óseas desde las de alto remodelado hasta las de bajo remodelado está alineada con la presencia de un mayor riesgo de calcificación vascular (CV), morbilidad y mortalidad en la población sometida a diálisis. La atenuación de las grandes expectativas anteriores en los quelantes cálcicos del fósforo y los análogos de vitamina D conlleva una nueva estrategia de tratamiento para mantener la salud ósea y vascular. De esta forma, se presenta una nueva justificación para el tratamiento de la EOA con diferentes tipos de quelantes que no contengan calcio y con hemodiálisis con calcio bajo. El tratamiento con Sevelamer ha reducido la concentración de calcio y aumentado los niveles de PTH, obteniendo como resultado la mejora de los marcadores de remodelado óseo, el aumento de la formación ósea y una mejora de la arquitectura trabecular, de forma que la progresión de CV se ralentiza aún más. Los datos sobre los beneficios del lantano en la histología de la EOA se han extraído de estudios clínicos a largo plazo. Aunque tras la interrupción del tratamiento, se produce una liberación lenta de lantano de los depósitos óseos y no existe relación con la toxicidad a nivel óseo similar a la del aluminio, el debate científico sobre su potencial tóxico a largo plazo sigue abierto. Finalmente, se ha demostrado que reducir el número de quelantes cálcicos y el nivel de calcio en la hemodiálisis (1,25 mmol/l) tiene repercusiones en la evolución hacia los marcadores que reflejan un remodelado óseo mayor. Por tanto, la adopción de quelantes que no contienen calcio debería reservarse a los pacientes con EOA de alto riesgo y progresión de calcificaciones vasculares asociadas con una mayor morbi-mortalidad.

Palabras clave: *Enfermedad ósea adinámica. Quelantes cálcicos de fósforo. Hemodiálisis con calcio bajo. Quelantes de fósforo que no contienen calcio.*

INTRODUCTION

Many nephrologists are reluctant to perform bone biopsy, although it has been considered as golden standard and diagnostic tool in identifying the type of bone diseases in chronic kidney disease (CKD) – mineral and bone disordered

patients.[1] Four types of renal osteodystrophy can be distinguished: low turnover osteomalacia (OM) and adynamic bone disease (ABD), hyperparathyroid bone disease (HPTH) and mixed lesion (Mx), even before dialysis treatment is started.[2] Over the last two decades the prevalence of ABD has been increased in dialysis and peritoneal dialysis patients, as well as in CKD populations, and nowadays represents the most frequent type of bone lesion.[3,4] In addition to diabetes and older age of patients coming to dialysis as fixed factors, calcium-based binders, vitamin D analogues, and a high calcium dialysate are pointed out as important modifiable factors associated with development of ABD.[5] Indeed, the use of calcium-based binders in combination with vitamin D analogues, has been shown to lead to an over-suppression of parathyroid hormone (PTH) and development of low-bone turnover ABD.[6,7] Thus, a change in paradigm occurred lately whereby not hypocalcemia but hypercalcemia and positive calcium balance were considered negative factors. The changing prevalence of various types of bone diseases from a high to low-bone turnover goes in line with the presence of increased risk for vascular calcification, morbidity and mortality in the dialysis population.[6,7]

The attenuation of the previous great expectations in calcium-based phosphate binders and vitamin D-analogues entailed a new treatment strategy to preserve bone and vascular health. Hence, a new treatment approach as prevention of complications of therapy in order to maintain mineral homeostasis and bone health was proposed.[8,9] Furthermore, a new evidence for treatment of ABD with various types of non calcium based binders and low calcium dialysate is presented.

SEVELAMER HYDROCHLORIDE IN TREATMENT OF ABD

In a post- hoc analysis of thoracic vertebral bone attenuation in patients treated for 1 year in the Treat-to-Goal study, there has been a significant decrease in trabecular bone attenuation in calcium-treated patients, and a trend towards increased bone attenuation in sevelamer-treated patients.[10] The between-group differences in trabecular bone attenuation have been statistically significant *(P*=0.01). The lower time averaged PTH in association with higher concentrations of serum calcium achieved in calcium-treated subjects is a likely explanation for the changes observed in bone attenuation.

Recently, improved bone histology of ABD patients treated by sevelamer has been reported by Ferreira et al.[11] Although sevelamer treatment has failed to improve bone turnover or mineralization compared with calcium carbonate, bone formation has been significantly increased and trabecular architecture improved in the sevelamer group. This might be in line with the inert nature of ABD in which the bone histology needs a potent and sustained stimulus in order to get an improvement which occurs very slowly. However, changes in biochemical markers of bone turnover may forecast improvements in bone histology, as it was reported in the Japanese dialysis population with low PTH levels treated with sevelamer.[12] The reduced serum calcium concentration and thereby increased PTH levels under sevelamer treatment has resulted in improvement of all markers of bone turnover. Hence, it might have been concluded that the administration of sevelamer might improve the bone remodelling activity even in hemodialysis patients with diabetes (n=14).

LANTHANUM CARBONATE (LC) BENEFICIAL EFFECT ON ABD HISTOLOGY

A few study reports on treatment with lanthanum have shown its beneficial effect on bone histology. Namely, there has been a normalization of the bone histomorphometric parameters and almost no evolution toward low bone turnover after 1-year of treatment with lanthanum.[13] An additional follow up in a subset of patients (n=20) showed there is a slow release of lanthanum from its bone deposits 2 years after discontinuation of the treatment, but no association with aluminium-like bone toxicity could have been observed.[14] Finally, a similar phosphate control with calcum vs. lanthanum has resulted in a higher bone turnover after 1 year and a higher bone volume after 2 years with LC. Bone turnover has been low in 58% of patients at baseline in the LC group and in 35.5% of patients after 1-year of treatment, while bone volume has been low at baseline in 28% of patients and in only 9.4% after completion of 2 years of LC therapy.[15] In between group comparison, percentage of patients in the 1-year LC group with improvement in activation frequency and bone formation rate/bone surface has been significantly higher ($p < 0.05$) than in the calcium group (52.0 and 41.9%, respectively vs. 23.3 and 15.6%, respectively). Thus, there has been a substantial evidence to conclude lanthanum treatment might have been a preferable option in patients with adynamic bone disease.

LOW CALCIUM DIALYSATE AS AN OPTION TO TREAT ABD

Assessing the effect of lowering dialysate calcium on episodes of hypercalcemia, serum PTH levels and bone turnover, 51 CAPD patients with bone biopsy-proven ABD were randomized to treatment with control calcium (1.62 mM), or low calcium (1.0 mM) dialysate fluid over a 16-month period.[16] The low-calcium group has experienced a decrease in serum ionized calcium levels, reduced rate of hypercalcemic episodes, and 300% increase in serum iPTH values. Repeat bone biopsies after 16 months have shown that the low-calcium bath has led to a normalization of BFR and an improved ABD histology in 40% of patients at the end of the study. Yet, there has been a lack of biopsy proven

evidence of low calcium dialysate treatment in ABD patients. Nevertheless, an indirect effect as evolution towards parameters reflecting higher bone turnover in patients treated for 6 months with dialysate calcium of 1.25 mmol/l has been recently reported.[17] It occurs most likely by prevention of a positive calcium balance and enabling sustained stimulation of PTH secretion, but it should be confirmed in a bone biopsy based studies.

CONCLUSIONS

Reducing the number of calcium-based binders to only 1g per main meal/daily and a low calcium dialysate (1.25 mmol/l) should be an immediate preventive treatment in order to attenuate the indirect harmful effect of ABD on vascular calcification progression in dialysis patients. There is scarce evidence that this baseline therapeutical approach could even improve ABD histology. While waiting further biopsy based evidence in this regard, adoption of the non calcium-based binders should be reserved for ABD patients with a high risk of fractures and progression of vascular calcifications associated with increased morbidity and mortality.

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