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NEW ASPECTS OF TREATMENT OF RENAL BONE DISEASE IN DIALYSIS PATIENTS

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Abstract: The abnormalities in bone and mineral metabolism in chronic kidney disease patients are associated with an increased risk of fractures, vascular calcifications and cardiovascular diseases. A few decades ago hyperphosphatemia and the common development of secondary hyperparathyroidism were thought to be the main problem to deal with. Since dietary phosphate restriction and haemodialysis were not proven to be sufficient measures to reduce phosphorus, phosphate-binding therapy has been widely instituted as a treatment option. Various types of phosphate binders employed over the years have contributed to the changing spectrum of renal osteodystrophy from high to low bone turnover along with the shift from hypocalcemia and negative calcium balance towards hypercalcemia and the positive calcium balance. Thus, hypercalcemia instead of hyperphosphatemia is nowadays associated with the increased risk of vascular calcification, morbidity and mortality in the dialysis population,.

Besides the very expensive non-calcium based phosphate binders, at least two common tools may be helpful in the treatment of hypercalcemia and adynamic bone. A reduced daily use of calcium carbonate/acetate up to 1g per main meal is an easily manageable and inexpensive tool. The second option for stimulation of parathyroid gland activity and bone turnover is the lowering of the dialysate calcium concentration. In conclusion, an aggressive treatment of hyperphosphatemia and calcium overload might lead towards an opposite effect of hypoparathyroidism and hypercalcemia. Reasonable treatment strategies based on a careful monitoring should be employed in order to prevent related consequences and to contribute to a better long-term quality of life and survival of dialysis patients.

Key words: adynamic bone disease, vascular calcifications, calcium phosphate binders, low dialysate calcium concentration.

Pathophysiology of bone and mineral metabolism in uremia

The reduction of renal function in chronic kidney disease (CKD) patients alters the excretory and metabolic capacities of the kidney, producing a cascade of mineral and bone disorders (MBD) also known as renal osteodystrophy (ROD) [1]. Hence, the reduction in phosphate excretion in the early stage of CKD and consequently higher serum phosphate levels lead to a common development of secondary hyperparathyroidism (sHPTH) [2]. This compensatory sHPTH has been explained by three possible theories on phosphate retention and an initial promotion of PTH release: the induction of hypocalcemia [3], decreased formation or activity of calcitriol [4], and a direct effect of hyperphosphatemia to increase the PTH gene expression [5]. Thus, disturbances of calcium and phosphorus metabolism, impaired action of vitamin D and altered PTH response ultimately lead to a loss of the bone and mineral homeostasis and the development of renal osteodystrophy. This term encompasses five types of bone disease even before dialysis treatment is started: osteomalacia (OM), adynamic bone disease (ABD), hyperparathyroid bone disease (HPTH; either mild HPTH or osteitis fibrosa), mixed lesion (MX), and normal bone [6].

Clinical relevance and consequences

The abnormalities in bone and mineral metabolism in CKD patients are associated with an increased risk of fractures [7], vascular calcifications (VC) and cardiovascular diseases (CVD) [8, 9]. In addition, these disorders are an important cause of decreased quality of life and increased morbidity and mortality [10, 11]. In CKD patients, VC occurs more frequently and progresses more rapidly than in the general population [8] and cardiovascular mortality is exponentially increased with age, being up to 500 times higher than in the general population [12]. Importantly, the number of arteries calcified is reported to be an independent risk factor for cardiovascular disease and mortality in addition to the established conventional risk factors [13]. Hence, the growing worldwide public-health problem of CKD and related vascular problems raise consequences which are not related merely to the clinical bedside, but also represent a substantial socio-economic burden for the health-care system and the medical society itself.

Prevention and management of hyperphosphatemia and CVD

Hyperphosphatemia contributes to increased mortality in dialysis patients through an initiation and progression of VC (elevated calcium-phosphate product as a combination of marked hyperphosphatemia and normal or even

low-normal serum calcium concentration) [14, 15]. On the other hand, the deleterious consequences of prolonged hypersecretion of PTH in response to hyperphosphatemia have been reported along with hyperparathyroid bone disease as the most prevalent type of ROD during 70s [16]. In view of the need to control hyperphosphatemia a variety of modalities have been adopted in an attempt to prevent this complication, such as reduction in dietary intake, removal by dialysis, and phosphate binding and excretion through the intestine and guts.

The recommended dietary phosphate restriction is often complicated because of the patient's nonadherence to the diet or compromised protein intake and the nutritional status of the patient [17]. On the other hand, it has been shown that haemodialysis does not adequately clear phosphorus since it does not provide sustained control of serum phosphate levels. It has been shown in a kinetic study that during the first 2 hours of dialysis phosphate levels were reduced to almost half of the pre-dialysis value, with a negligible decline until the end of the session and an immediate rebound and rise by almost 40 % of the end-dialysis value at the end of the next two hours [18]. Since the first two modalities of treatment could not manage the complex interrelationship between hyperphosphatemia, calcium, PTH, vitamin D and nutritional status, a clear need for phosphate binding therapy has been established.

Aluminum hydroxide was instituted as a first line phosphate binding therapy in the early 1970s [19]. Further progress in the prevention of sHPTH was achieved with the institution of calcitriol therapy (peroral or parenteral) that became available on the market during the 1980s [20]. In the meanwhile, although very effective, it was shown that aluminum-containing compounds were associated with an accumulation in the body and the development of encephalopathy and/or microcytic anemia as well as low-turnover bone diseases (osteomalacia or adynamic bone), [21, 22]. Hence, ABD has been reported as the most prevalent lesion over the last two decades [23, 24].

At the beginning of 1990s, calcium carbonate (CC) became the most widely used phosphate binder as an efficient and inexpensive drug [25]. Nevertheless, a high intake of dietary calcium in the form of phosphate binders has been linked to an increased level of coronary calcification [8]. Moreover, it was recently reported that calcium-based binders, particularly when used in combination with vitamin D analogues, might lead to an over-suppression of PTH and development of ABD [26]. Hence the existence of ABD as the most prevalent form of ROD in recent years and its reduced ability to handle an exogenous calcium load has implied a higher risk of extra-osseous calcifications [27]. It seems that changes in the use of phosphate binders and vitamin D over the last few decades have contributed to the changing spectrum of ROD from high to low bone turnover along with the shift from hypocalcemia and a negative calcium balance towards hypercalcemia and a positive calcium balance.

Prevention and management of hypercalcemia and ABD

In order to reduce the calcium load from calcium-based phosphate binders a new group of calcium-free phosphate binders (sevelamer hydrochloride and lanthanum carbonate) has recently appeared on the market. The reduction of the calcium load was assumed to be as much as 9 gr/week if on average 5g/day calcium carbonate/acetate were used and only 20–30% reabsorbed as elemental calcium from the gut.

The shift in the paradigm towards hypercalcemia and adynamic bone was confirmed in our bone biopsy study in 84 Macedonian CKD patients where ABD was found as the most frequent bone lesion observed in 23% of the cases [6]. Besides male gender and diabetes, serum and bone calcium levels as well as calcium x phosphorus product were found to be increased in ABD patients in comparison with the decreased levels in OM patients, which helps further differentiation between these two low bone turnover conditions. Here, calcium carbonate was the only phosphate binder used in more than 50% of our pre-dialysis patients.

A recent study with lanthanum carbonate as a new phosphate binder has shown its safety and effectiveness in phosphate binding [28]. Again, after the group with mixed bone lesion, ABD was found to be the second most prevalent, in 19% of patients at baseline biopsy. When the effect of lanthanum carbonate (LC) and calcium carbonate (CC) on the evolution of renal osteodystrophy in dialysis patients was compared after one year of treatment, the bone histomorphometry in the lanthanum group resulted in a smaller number of ABD patients (9%) in comparison with the baseline biopsy (18%), while the patients treated with calcium carbonate showed an evolution towards low bone turnover from baseline to the one-year follow-up (20% vs. 30%). Here, the association between the calcium-based phosphate binder and the development of ABD after one year of treatment was clearly demonstrated. In contrast, lanthanum carbonate was shown to be an effective phosphate binder with almost no evolution toward low bone turnover at the one-year follow-up. Additionally, there was no suggestion of the adverse bone effects previously reported for aluminum hydroxide.

When an extension of the aforementioned study in a subset of patients (n = 19) from our centre was carried out, the third biopsy after a two-year additional follow-up on calcium carbonate showed an increase in the number of ABD patients from 15% at baseline and one year to 26% at the end of the two-year follow-up [29]. Actually, ABD was found to be the most prevalent bone disease at the end of the two-year follow-up on calcium carbonate, whereas HPTH was diagnosed in only 5% of patients.

Nowadays, a reasonable strategy for managing hypercalcemia and ABD should rely on the correctable factors, such are: hyposphosphatemia, hypercal-

cemia and hypoparathyroidism, mainly due to the higher intake of calcium salts and calcitriol and the use of high calcium dialysate [23, 26, 30, 31]. Hypophosphatemia and hypercalcemia can be involved in the pathogenesis of low bone turnover by reducing PTH secretion. In this particular case, a strict recommendation of protein restriction is not needed, whereas careful monitoring of the daily calcium load from food and calcium salts ingestion is advisable. Calcium acetate and carbonate are inexpensive, efficient phosphate binders but their extended and/or inappropriate use leads to an excessive absorption of elemental calcium, increased serum calcium, over-suppressed PTH and, ultimately, promotion of soft-tissue and vascular calcification, especially under the low bone turnover conditions. Hence, it seems reasonable sometimes to reduce the number of calcium carbonate/acetate tablets to only 1g per main meal/daily in order to increase serum phosphate and decrease serum calcium, which both in turn might positively stimulate PTH secretion. This manoeuvre is relatively easy to manage in comparison with the efficient and potentially harmless, but very expensive non-Al, non-Ca based binders such as lanthanum carbonate and sevelamer hydrochloride [32, 33].

In the case of ABD, calcitriol therapy is not desirable because of the risk of inducing hypercalcemia, extraosseous calcifications and further suppression of parathyroid gland activity. In addition, the use of a low calcium dialysate is recommended as a strategy to increase PTH levels and possibly to normalize bone turnover in patients with ABD [34]. Low calcium dialysate (1.25 mmol/l) was reported to have an impact on the evolution towards markers reflecting higher bone turnover, most probably by prevention of a positive calcium balance, enabling sustained stimulation of PTH secretion [35]. The treatment is safe and without any major adverse effects, and considered as a valuable therapeutic option for ABD patients. However, the balance of calcium should be maintained very carefully, especially in older patients prone to osteoporosis and hip fracture. Here, calcium mineralization of the bone would not be possible without an activation of bone formation. Hence, the bone turnover should be increased through stimulation of the parathyroid gland activity first and then a positive calcium balance should be subsequently reinforced.

Conclusions

While a few decades ago hyperphosphatemia and the fequent development of secondary hyperparathyroidism were presumed to be the main problems to deal with, hypercalcemia and ABD have nowadays been associated with an increased risk of vascular calcification, morbidity and mortality in the dialysis population.

Besides the very expensive non-calcium based phosphate binders, a reduced daily dose of calcium carbonate/acetate up to 1g and a lowering of the dialysate calcium concentration are proposed as common tools to cope with the problem. In conclusion, an aggressive treatment of hyperphosphatemia and calcium overload might lead to the opposite effect of hypoparathyroidism and hypercalcemia. Reasonable treatment strategies based on careful monitoring should be employed in order to prevent related consequences and to contribute to a better long-term quality of life and the survival of dialysis patients.

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Резиме

НОВИ АСПЕКТИ ВО ТРЕТМАНОТ НА БУБРЕЖНИТЕ КОСКЕНИ ЗАБОЛУВАЊА КАЈ ПАЦИЕНТИТЕ НА ДИЈАЛИЗА

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Абнормалностите во метаболизмот на минералите и коските кај пациентите со хронични бубрежни заболувања се асоцирани со зголемен ризик за фрактури, васкуларни калцификации и кардиоваскуларни заболувања. Пред неколку декади хиперфосфатемијата и вообичаениот развој на секундарен хиперпаратироидизам претставуваа главен проблем кој требаше да биде решен. Откако рестрикцијата на фосфорот во исхраната и хемодијализата се покажаа како недоволно ефикасни мерки за намалување на фосфорот, третманот со фосфор-врзувачи стана широко имплементирана терапевтска опција. Различните типови на фосфор-врзувачи, употребени во текот на изминатите години, придонесоа за промени во спектрумот на реналната остеодистрофија од коскена болест со висок кон коскена болест со низок обрт и пренасочување од состојбата на хипокалцемија и негативен калциумски баланс кон состојба на хиперкалцемија и позитивен калциумски баланс. Така {то, денес, всушност, хиперкалцемијата наместо хиперфосфатеми-

јата е асоцирана со зголемен ризик за васкуларни калцификации, морбидитет и морталитет кај дијализната популација.

Освен многу скапите не-калциумски фосфор врзувачи, барем две вообичени терапевтски опции можат да помогнат во третманот на хиперкалцемијата и адинамичната коска. Редуцираната дневна употреба на калциум карбонат/ацетатот до 1 гр во тек на главниот оброк е лесно изводлива и евтина опција. Втора можност за стимулација на активноста на паратироидната жлезда и коскениот обрт е намалувањето на концентрацијата на калциумскиот дијализат. Како заклучок, агресивниот третман на хиперфосфатемијата и оптоварувањето со калциум може да доведе до спротивен ефект на хипопаратироидизам и хиперкалцемија. Потребни се разумни терапевтски стратегии, базирани на внимателно следење, за да се превенираат соодветните консеквенци и да придонесат за подобар и долготраен квалитет на живот и преживување на пациентите на дијализа.

Клучни зборови: адинамична коскена болест, васкуларни калцификации, калциумски врзувачи на фосфор, дијализат со ниска концентрација на калциум.

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