CHRONIC KIDNEY DISEASE-MINERAL BONE DISORDER IN THE ELDERLY PERITONEAL DIALYSIS PATIENT

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♦ **Purpose:** The purpose of this paper was to review the literature concerning the treatment of chronic kidney disease-mineral bone disorder (CKD-MBD) in the elderly peritoneal dialysis (PD) patient.

♦ **Results:** Chronic kidney disease-mineral bone disorder is a major problem in the elderly PD patient, with its associated increased fracture risk, vascular calcification, and accelerated mortality fracture risk. Peritoneal dialysis, however, bears a lower risk than hemodialysis (HD). The approach to CKD-MBD prophylaxis and treatment in the elderly PD patient is similar to other CKD patients, with some important differences. Avoidance of hypercalcemia, hyperphosphatemia, and hyperparathyroidism is important, as in other CKD groups, and is generally easier to attain. Calcium-free phosphate binders are recommended for normocalcemic and hypercalcemic patients. Normalization of vitamin D levels to $> 75 \text{ nmol/L}$ ($> 30 \text{ pg/L}$) and low-dose active vitamin D therapy is recommended for all patients. Hyperparathyroidism is to be avoided by using active vitamin D and cinacalcet. Particular attention should be paid to treating protein malnutrition. Fracture prophylaxis (exercise, use of walkers, dwelling modifications) are important. Hypomagnesemia is common in PD and can be treated with magnesium supplements. Vitamin K deficiency is also common and has been identified as a cause of vascular calcification. Accordingly, warfarin treatment for this age group is problematic.

♦ **Conclusion:** While treatment principles are similar to other dialysis patient groups, physicians should be aware of the special problems of the elderly group.

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While treatment of renal osteodystrophy was previously concentrated mainly on the prevention of fractures and metastatic calcification, focus in recent years has moved to the prevention of vascular calcification. The 2 problems are closely connected since control of calcium, phosphate, parathyroid hormone (PTH), and vitamin D are integral to the prophylaxis of

both diseases. Renal osteodystrophy is therefore now referred to as chronic kidney disease-mineral bone disorder (CKD-MBD). The 2 major bone diseases in dialysis are low bone turnover (adynamic bone disease [ABD]) and high bone turnover, usually caused by secondary hyperparathyroidism. The problems encountered by the elderly peritoneal dialysis (PD) patient are essentially the same as for the elderly hemodialysis (HD) patients. Guidelines for the treatment of CKD-MBD have been published, both by Disease Outcomes Quality Initiative (DOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) (1,2), and these guidelines are applicable to elderly patients. Elderly PD patients differ from younger HD patients in the following ways:

- 1) The prevention of hypercalcemia, hyperphosphatemia, and hyperparathyroidism is generally easier in the elderly due to lower nutritional intake of calcium and phosphate and involutional changes in bone turnover.
- 2) The prevalence of ABD is higher in PD (3). This may, however, have changed in recent years due to a reduction in dialysate calcium from 1.75 to 1.25 meq/L.
- 3) The risk of fracture is higher in the elderly and in females. The incidence of hip fractures in dialysis patients is 4 – 5 times higher than in the general population (4,5), rising to 9 times after 4 years of dialysis. Risk varies between 0.5 and 1.5%/yr (5–7), and overall fracture incidence between 1.2 and 4.5%/yr (7). Vertebral fractures are also common. Elderly patients are at particular risk of hip fractures with rates of 3.3 – 4.7%/year (5,8). Fracture rates have fallen since 2004 (8). Mortality rates in excess of 50% are seen among elderly patients in the first year after a fracture (7). Fracture incidence in HD is 1.3 – 1.5 times higher than PD (7,9) either due to higher fall rates associated with postural hypotension after HD, better preserved bone microarchitecture in PD (10), or higher bone mass density (BMD) (11).
- 4) The risk of protein energy wasting (PEW), often referred to as malnutrition, is higher in the elderly, with associated reduced bone mass (12) and increased fracture risk (7).
- 5) The risk of vitamin D deficiency is higher, possibly due to increased loss of vitamin D in the dialysate (13,14). Many patients in PD will have preserved residual renal function; in the presence of nephrotic syndrome, vitamin D reserves will be depleted (14).

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THE PROPHYLAXIS OF CKD-MBD

DIET

The prevention of hyperphosphatemia by dietary phosphate restriction is mandatory. However, PEW must be avoided, and since protein contains 15 mg phosphate per gram phosphate, compromise may be necessary. The patient new to PD will usually have an adequate protein intake (> 1 g/kg/day), but as residual renal function falls, protein intake will also fall. Peritoneal dialysis patients lose 6 – 10 g protein/day via dialysate, and ambitious targets of protein intake (1.1 – 1.2 g/kg/day) have therefore previously been recommended for PD patients. However, this implies that increased protein intake automatically prevents PEW. Ingested protein is metabolized to amino acids, which are then synthesized to new protein in the liver. Elderly patients will have a reduced hepatic function, and may not be able to utilize the amino acid load. The net result may just be increased acidosis and nausea. Furthermore, the excess risk of hypoalbuminemia due to PD therapy does not seem to be harmful (15). Trials of increased protein intake, either by dietary protein supplements or amino acid-containing dialysate have been disappointing (16,17). Ambitious targets are usually unrealistic, even in motivated patients, and a more modest goal, e.g. > 0.8 g/kg/day, is advisable.

DIALYSIS

Conventional guidelines for dialysis adequacy concentrate on urea clearance (Kt/V), but since phosphate clearance in PD is closely correlated to creatinine clearance, this is more important for phosphate control. A total creatinine clearance of > 5 mL/min is advisable. This may be difficult to attain in the anuric slow transporter.

PHOSPHATE BINDERS

In the absence of randomized controlled trials, recommendations are based on epidemiological and theoretical grounds. Both low and high values of calcium, phosphate, and parathyroid hormone (PTH) are associated with increased mortality (18). The high mortality associated with hypophosphatemia is probably because it is a marker of PEW, while hyperphosphatemia causes phenotypic conversion of smooth muscle cells to osteoblasts and is probably a major cause of vascular calcification. Kidney Disease Outcomes Quality Initiative (KDOQI) recommends a goal of < 5.5 mg/dL (< 1.8 mmol/L), while KDIGO recommends normalization. Many phosphate binders are available, and are more or less equally potent. They can either be calcium-containing (calcium carbonate, calcium acetate) or calcium-free (sevelamer hydrochloride, sevelamer carbonate, lanthanum, magnesium carbonate). A combination of calcium acetate and magnesium carbonate is commercially available, and gives a lower calcium load than other calcium-containing products. The

iron-containing phosphate binder sucroferrioxhydroxide has recently been marketed.

Despite a plethora of controlled studies, the role of plasma calcium levels on the clinical effects of phosphate binders has not been investigated. Clearly, hypercalcemia is contraindicated, so calcium-containing binders are contraindicated here. Calcium-containing binders or a high calcium dialysate are chosen in the presence of hypocalcemia, with its increased risk of cardiac arrhythmias and hyperparathyroidism. The choice of phosphate binder in normocalcemic patients is more difficult. All binders are associated with gastrointestinal side effects (sevelamer carbonate less than sevelamer hydrochloride), and avoidance of these is a major factor in drug choice. An additional problem may be economic, since calcium-free binders are generally expensive. A large study failed to demonstrate any difference in mortality between calcium carbonate and sevelamer hydrochloride (19). However, a subgroup analysis showed lower mortality for sevelamer in elderly patients, suggesting that calcium-free phosphate binders may be helpful in elderly normocalcemic PD patients.

CALCIUM

The concept that vascular calcification is caused by hypercalcemia and hyperphosphatemia, with consequent precipitation of calcium phosphate in the vasculature is simplistic. The uremic state is characterized by increased levels of a number of calcification promoters (e.g. Type 1 collagen, BMP2, core binding factor, TNF β) and reduced levels of inhibitors (Matrix Gla protein [MGP], fetuin A, BMP7, osteoprotegerin). Still, hypercalcemia is probably a cause of vascular calcification and therefore contraindicated. This is relatively easy in the elderly patient, using calcium-free phosphate binders, reduced dose of active vitamin D, and low-calcium dialysate (1.25 mM). Low calcium is also associated with increased mortality; whether this is causal, or just another marker for PEW is unclear. Similarly, it is not certain whether normalization of mild hypocalcemia is beneficial, or whether the obligate hypocalcemia associated with cinacalcet requires treatment.

PARATHYROID HORMONE

The range of PTH associated with the lowest mortality and most normal bone turnover is 150 – 300 ng/L (ca. 15 – 30 pmol/L). This is higher than in the general population, due to skeletal resistance to PTH and the presence of inactive metabolites in the analysis. Secondary hyperparathyroidism is causally associated with increased bone loss (particularly in the axial bones), extraskeletal calcification, muscle weakness and anemia. Conventionally, fracture risk is associated with both high and low levels of PTH (20), but a recent large study showed no relationship below 900 ng/L. The present review is in accordance with the KDOQI guidelines (1) and recommends an upper limit of 300 ng/L, primarily using active vitamin D. There are no proven differences between the various drugs available (21), choice being mainly determined by price. Resistant cases

can be treated with cinacalcet, a calcimimetic, which reduces PTH by about 40%, even in patients with severe secondary hyperparathyroidism. For the elderly patient, medical treatment is preferred to surgical parathyroidectomy.

It is not clear whether ABD, which is characterized by low PTH (< 150 ng/L), and also associated with increased mortality, should be treated, usually by inducing hypocalcemia, with an accompanied risk of BMD loss (22). Adynamic bone disease results in a reduced buffer function, with attendant risks of hypercalcemia, which is contraindicated. Adynamic bone disease is found in PD patients, elderly patients, patients with high comorbidity and/or PEW, and diabetics, even in the presence of normal renal function (23). It is unlikely that the disease is iatrogenic (due to calcium and active vitamin D therapy), since these patients do not require intensive medical treatment. It is more likely that it is a marker of PEW and involutional changes (11,24). Improvements in protein status alone are sufficient to cure ABD (25). It has been suggested that increased sclerostin expression causes ABD in a PTH-independent manner (10).

VITAMIN D

The level of 25-hydroxycholecalciferol (25-OHD) is almost universally reduced in dialysis, due to low exposure to sunlight and reduced dermal synthesis (14). In addition to its well-known detrimental effects on muscle function, falls risk, and bone (osteomalacia and osteopenia), 25-OHD deficiency is associated with a large number of disorders (e.g. hypertension, cardiac disease, cancer, diabetes, auto-immune diseases, immune deficiency, and diabetes). It is likely that some of these relations are causal. Therapy reduces PTH, even in CKD stage 5 (26). Vitamin D therapy is cheap and without side effects. Poisoning is unknown below 200 nmol/L (80 pg/L), due to controlled metabolism in the liver. A level of 75 nmol/L (30 pg/L) is the level associated with maximal PTH suppression, and is indicated in all patients. Peritoneal dialysis patients require higher doses (14): 25 – 35 $\mu\text{g/d}$ are usually necessary, and some patients will require 70 $\mu\text{g/d}$. Reduced muscle strength, a particular predictor of fractures, is improved by vitamin D in PD patients (14).

Active vitamin D is generally recommended in the presence of hyperparathyroidism. However, its use is being reevaluated after the introduction of cinacalcet, which, in contrast to vitamin D, tends to lower calcium and phosphate levels. In addition, a large number of studies have shown an inverse correlation between therapy and mortality, cardiovascular mortality, hypertension, vascular stiffness, and calcification (24,27). It is particularly remarkable that this effect is seen independently of PTH, calcium, and phosphate levels, suggesting that the conventional view of vitamin D as being contraindicated in ABD (28) is erroneous. Correlation does not prove causation, but theoretical studies suggest that these effects are causal (24). Randomized controlled trials have not been performed. A cautious approach would be to treat all dialysis patients with low-dose active vitamin D, e.g. alfacalcidol ≤ 0.25 $\mu\text{g/d}$, calcitriol ≤ 0.25 $\mu\text{g/d}$ or paricalcitol

≤ 1 $\mu\text{g/d}$ (29). This will also reduce the number of falls by 50% in elderly uremic patients (30).

MAGNESIUM

While hypermagnesemia previously was a feared complication of renal failure, recent research has drawn attention to the greater threat of hypomagnesemia. It is associated with increased mortality, PTH, hypertension, metabolic syndrome, type 2 diabetes, and increased vascular calcification. Magnesium supplements reduce intima media thickness and slow vascular calcification (31). Elderly PD patients are at particular risk for hypomagnesemia, particularly after long-term PD, due to PEW and the fact that low levels of magnesium (0.25 meq/L) in the dialysate result in a negative magnesium balance. Control of magnesium levels in the blood is indicated, and hypomagnesemia corrected with magnesium supplements, e.g. as part of a phosphate binder regime. A large number of products are available using various cations (oxide, carbonate, acetate, citrate), with varying side effects, principally diarrhea in 1 – 10%. The patient with side effects would be well advised to shop around.

ACIDOSIS

Acidosis is a cause of bone disease, and relatively contraindicated (32). This is rarely a problem in PD, except when patients are being treated with amino acid solutions, where sodium bicarbonate supplements may be necessary.

WARFARIN

The anticoagulant effect of warfarin is due to vitamin K1 (phyloquinone) depletion. Warfarin has been implicated as a cause of calciphylaxis and vascular calcification. Matrix Gla protein (MGP), a calcification inhibitor, requires γ -carboxylation for activation, and this in turn requires vitamin K. Activation of vitamin K is also by γ -carboxylation, which is inhibited by warfarin. Dialysis patients have low levels of vitamin K1 and K2 (menaquinone), and this is predictive of an increased fracture rate and vascular calcification (33). Warfarin treatment is often difficult in dialysis patients with an increased risk of bleeding and is relatively contraindicated in elderly PD patients. In the absence of studies showing anti-apoplectic effect of warfarin on dialysis patients with atrial fibrillation, caution is advised in treating patients for this indication. It is unknown whether combination of warfarin and vitamin K2 supplements would remove this problem. Whether vitamin K supplements are therapeutic for PD patients is unknown.

FIBROBLAST GROWTH FACTOR 23

An important new hormone involved in the control of CKD-MDB is the phosphaturic hormone fibroblast growth factor 23 (FGF23). Levels are massively increased in dialysis patients. Secretion from osteocytes is stimulated by phosphate, PTH

and 1,25-dihydroxycholecalciferol (1,25-OHD). Fibroblast growth factor 23 reduces phosphate in patients with significant residual renal function, suppresses PTH and 1,25-OHD production, and causes left ventricular hypertrophy.

Klotho is a gene whose absence is associated with accelerated aging. Klotho expression is downregulated in uremia. Fibroblast growth factor 23 is required to activate FGF signaling and is associated with increased mortality. It is unknown whether this is because raised FGF23 is just a marker of hyperphosphatemia or Klotho deficiency, secondary to left ventricular hypertrophy, or due to other causes. There are no current therapeutic recommendations related to FGF23.

PREVENTION OF FRACTURES

The risk of fractures is particularly high in the elderly frail patient, even with optimal prophylaxis, partly because most patients will start dialysis in an osteopenic state due to long-standing uremia. The risk of falls exacerbates the problem. Suitable changes to the patient's dwelling may be necessary, and the patient should be encouraged to use a walker when outdoors. Exercise is encouraged (6,34,35). Probably the best prophylaxis for the elderly PD patient is a reduction in psychoactive drug use, which increases fracture risk by 30–70% (36).

Prediction of fractures is generally difficult. Biochemical variables are of little use. Bone mass density measurements using dual energy x-ray absorptiometry (DEXA), for example are highly predictive of fracture rates in the general population, but less so in dialysis patients, although patients with fractures do have a significantly lower BMD, particularly at the radius, where BMD is 1.24 standard deviations lower (35). The patient with a low T-score at the radius or with a rapidly falling Z-score would thus seem to be at increased risk. However, since a bone biopsy is necessary to identify the correct diagnosis and treatment in this situation, the usefulness of routine DEXA measurements is dubious.

KEY POINTS

Recommended prophylactic and therapeutic interventions for CKD-MBD in the elderly PD patient:

- Prevention of hypo- and hypercalcemia by appropriate dose of active vitamin D and dialysate calcium concentration
- Prevention of hypomagnesemia with magnesium supplements
- Vitamin D supplements to achieve 25-OHD >75 nmol/L (>30 pg/L)
- Low-dose active vitamin D to all patients
- High protein intake, minimum >0.8 g/kg/day
- Exercise and physiotherapy

DISCLOSURE

The author has no financial conflicts of interest to declare.

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