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REVIEW

Bone disease in elderly dialysis patients

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Abstract

Bone disease is a well-known complication of chronic kidney disease. Bone fracture risk is increased in dialysis patients, particularly in the elderly. Secondary hyperparathyroidism is an important factor, but increased bone fragility can not only be explained by increased parathyroid gland activity. A new term, uremic or chronic kidney disease osteoporosis has been proposed. The diagnosis is not simple, and besides new densitometric methods, e.g. high resolution peripheral quantitative computed tomography (HR-pQCT), biochemical parameters and the adapted fracture risk assessment tool (FRAX) could be used. In addition to the classic treatment of renal osteodystrophy, new drugs like teriparatide or denosumab could be used. Unfortunately, randomized prospective studies of new drugs in dialysis patients are lacking. The incidence of bone fractures, diagnosis of osteoporosis, and treatment of osteoporosis in dialysis patients is briefly described in this short review.

Key words: chronic kidney disease; renal osteodystrophy; osteoporosis

Introduction

Elderly people are susceptible to many chronic diseases such as diabetes mellitus, hypertension, chronic kidney disease (CKD), osteoporosis etc. CKD, defined as glomerular filtration <60 ml/min/1.73 m^2 or evidence of kidney damage for more than 3 months is a growing public health problem affecting about 10% of the general adult population [1]. Cardiovascular disease is the major complication of CKD. Besides traditional risk factors such as hypertension, dyslipidemia and smoking, mineral and bone disorders are important risk factors for cardiovascular disease in CKD.

The term renal osteodystrophy was first used in 1943 to describe bone disease associated with chronic renal failure [2]. Since then, the prevention and treatment of bone disease in CKD remains a great challenge for many nephrologists. Six decades later, broad basic and clinical research has been conducted. It was recognized that bone disease is only one of the consequences of disturbed mineral metabolism. Twelve years ago, a new definition was established: chronic kidney disease – mineral and bone disorder (CKD-MBD) [1]. It describes a very broad clinical syndrome, i.e. a systemic disorder of mineral and bone metabolism due to chronic kidney disease manifested by abnormalities of calcium, phosphorous, parathyroid hormone (PTH) and vitamin D; abnormalities in bone turnover, mineralization, volume, strength or linear growth as well as soft tissue and vascular calcification. Renal osteodystrophy is only a part of CKD-MBD. It is a multifactorial disorder of bone metabolism and is quantifiable by histomorphometry of bone biopsy. Based on bone histomorphometry, there are three major pathologic patterns of bone remodelling in CKD. High bone turnover disease is due to severe secondary hyperparathyroidism. Low bone turnover disease (adynamic or aplastic bone disorder), is often a result of an inadequately low level of parathyroid hormone. The third form is the so called mixed renal osteodystrophy, caused primarily by secondary hyperparathyroidism [3].

Osteoporosis is a disease characterized by low bone mass and microarchitectural changes of bone tissue, leading to enhanced bone fragility and increased fracture risk [4]. It is the most common metabolic bone disease in the general adult population. Risk factors for osteoporosis are gender, family history of bone fractures, previous fractures after low trauma, smoking and alcohol consumption, low body weight etc. Older age is also a very important risk factor. Increased risk of osteoporotic bone fractures is the consequence of low bone strength. Bone strength is defined by bone mineral density, i.e. bone quantity (measured as grams of mineral per area or volume) and bone quality (described by changes in microarchitecture, turnover, mineralization and damage accumulation) [5]. Due to the rising ageing population, the number of patients with osteoporosis and osteoporotic bone fractures is increasing.

Patients with CKD, and particularly dialysis patients, are also increasingly older. For example, the median age of patients on renal replacement therapy in Croatia in the year 2001 was 55 years, and in 2014 it was 67 years. Therefore, it is not surprising that there is an increased risk, incidence and prevalence of bone fractures in CKD patients. Besides typical bone disease i.e. renal osteodystrophy, osteoporosis due to increased age or gonadal hormone deficiency could be seen in CKD patients [6]. Moreover, if we accept the World Health Organization (WHO) definition of osteoporosis as fragility fracture or hip bone mineral density (BMD) T score of 2.5 or lower, the prevalence of osteoporosis could be higher in CKD patients than in the general population. It should be highlighted that low bone mass (i.e. osteoporosis) is very common in renal osteodystrophy. The negative balance between bone formation and resorption could be seen in high bone turnover and mixed bone lesions (increased bone formation and resorption but the resorption is much higher), and also in low turnover (low bone formation and resorption, but resorption is higher) [7]. The final result is lower bone densitometry, i.e. osteopenia or osteoporosis and increased risk of fractures. Finally, in CKD patients, especially the elderly, coexisting renal osteodystrophy and osteoporosis could be seen.

Bone fractures in dialysis patients

The higher risk, incidence and prevalence of bone fractures in stage 5 CKD and dialysis patients has been confirmed in several retrospective and prospective studies [8]. A multicenter cohort study in the USA showed that 13.6 female and 7.5 male patients had an incident hip

fracture among 1000 person-years. In the well-known DOPPS II study, that included more than 12000 patients, the prevalence of hip fracture was 8.9/1000 person-years [9]. In 767 haemodialysis patients from nine Croatian haemodialysis centres, a total of 36 fractures were recorded [10]. The prevalence of patients with bone fractures was 4.0%. Among all fractures there were 14 hip fractures (39%), eight forearm fractures (22%), five upper arm fractures (14%), four femur fractures (11%), two lower leg fractures (5%), and one rib, vertebrae and hand fracture, each (3%). In patients less than 40 years, no bone fractures were observed. Eight bone fractures (22%) were recorded in patients aged 41 to 60, and 28 bone fractures (78%) in patients older than 60 years [10].

There are several explanations why bone fractures occur more often in dialysis patients. First, there is well known frailty in CKD patients, myopathy and polyneuropathy, and therefore, increased risk of falls. Another contributing factor is bone disease. The quality of bone in CKD patients is impaired, i.e. there is a change in bone strength. A considerable number of CKD patients have a significantly reduced bone mineral density. It could be seen as the result of high and low bone turnover (see above) or as osteoporosis due to increased age, gonadal dysfunction and/or effect of uremic toxins. There are also changes in the bone extracellular matrix and microarchitecture [8,11].

Diagnosis of CKD-MBD and/or uremic osteoporosis

The KDIGO Working Group recommended measurement of serum PTH or bone-specific alkaline phosphatase to evaluate bone disease because markedly high or low values predict underlying bone turnover [1]. Bone alkaline phosphatase (BAP) is the bone formation marker and the level of BAP is not influenced by kidney function. A high PTH level (i.e. secondary hyperparathyroidism) correlates with high bone turnover. Bone resorption markers are not suggested as routine measurement.

There is an interesting opinion about densitometry. Based on four prospective studies of bone densitometry and incident fractures in CKD patients, the KDIGO Working Group suggests BMD testing to assess fracture risk if results will impact treatment decision. They suggest dual-energy X-ray absorptiometry (DXA) measures of BMD. In CKD patients, the accuracy of DXA may be low due to interference with soft tissue calcification. On the other hand, the PTH effect on cortical bone is well-known, therefore measurement of bone density on the appendicular part of the skeleton could be useful. Also, reporting the Z score could be useful. We need more experience with new methods, e.g. high-resolution peripheral quantitative CT (HR-pQCT) before routine clinical use [12,13,14].

The fracture risk assessment tool (FRAX) is not recommended in patients with CKD, at least by recent guidelines. However, in recent studies FRAX was associated with fracture risk in patients with CKD [11,15].

There is no doubt that bone biopsy and bone histomorphometry is the gold standard in diagnosis of bone disease in CKD. In recent guidelines, it is recommended to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions. We should keep in mind that it is an invasive, time consuming method, and very important present bone changes from one small part of skeleton and in precisely short time [1,3].

Our opinion is that the diagnosis of bone disease should be based on biochemical parameters (PTH, alkaline phosphatase), densitometry, bone X-rays, and in unclear cases bone biopsy. Also, although we need more data, it seems that FRAX could be useful in patients with CKD.

Prevention and treatment

The prevention and treatment of CKD-MBD is still a great challenge for nephrologists [16]. Today, we have a nice armamentarium of drugs in the prevention and correction of mineral disturbance in CKD: phosphate binders, vitamin D and vitamin D analogues, and calcimimetics [1,17]. These drugs could also have a positive effect on bone metabolism. On the other hand, there are also several drugs for the treatment of primary osteoporosis: bisphosohonates, teriparatide, denosumab, and selective estrogen receptor modulators (SERM) [15]. The KDIGO Working Group suggests that in patients with

biochemical abnormalities suggestive of CKD-MBD and low BMD and/or fragility fractures, the treatment choice should take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of bone biopsy. The problem is that some anti-fracture drugs are contraindicated in patients with a glomerular filtration <30 ml/min/1.73 m^2. Based on a few studies with bisphosphonates, it could be concluded that in dialysis patients their efficacy and safety is unclear [11]. Denosumab, an anti-receptor activator of nuclear factor kappa B is a relatively new drug for the treatment of osteoporosis. It could also be used in dialysis patients. No dose adjustment is needed but there is a high risk of severe hypocalcaemia. This can be prevented with the use of calcitrol and calcium replacement. Teriparatide, an anabolic drug, could be useful, especially in patients with low bone turnover. Romosozumab, a monoclonal antibody against sclerostin, could be useful in CKD patients with a low PTH level, i.e. adynamic bone disease, but once again, we need more clinical data for this new drug. Raloxifene, a SERM drug has an anabolic effect and could increase trabecular lumbar spine BMD. However, it must be administered with great caution in CKD patients [11,15].

Conclusion

Bone disease is one of the most common complications of CKD. There is a high incidence of bone fragility fractures in this group of patients. The high incidence is a result of the combination of renal osteodystrophy as a part of the CKD-MBD syndrome, and age-related osteoporosis. A multidisciplinary approach by various experts (nephrologists, endocrinologists, radiologists and orthopaedic surgeons) is desired in the diagnosis, prevention and treatment of CKD-MBD and uremic osteoporosis.

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