

Osteoporosis and adynamic bone in chronic kidney disease

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ABSTRACT

Among the chronic kidney disease–mineral bone disease (CKD-MBD) disorders, osteoporosis and adynamic bone are highly prevalent, and they have been consistently associated with low bone mass, bone fractures, vascular calcifications and greater mortality in general and CKD populations. Despite the fact that osteoporosis and adynamic bone have similar clinical outcomes, they have different pathogeneses and clinical management. In osteoporosis, there is a lack of balance between bone formation and bone resorption, and less new bone is formed to replace bone losses. Osteoporosis is defined by the World Health Organization as “a disease characterized by low bone mineral density and micro architectural deterioration leading to low bone strength and increased risk of fractures.” In the general population, there is a good correlation between dual-energy X-ray absorptiometry measurements and bone fractures, but this is not the case with CKD patients. Despite the fact that we have a great number of active antiosteoporotic drugs, the experience in CKD patients is limited. Adynamic bone is suspected based on biochemical parameters, mainly parathyroid hormone (PTH) and bone alkaline phosphatase, but it needs to be proven using a bone biopsy, where a low or zero bone formation rate and a reduction or absence of osteoblasts and osteoclasts should be found. The clinical management of adynamic bone has important limitations and currently does not allow taking many active measures. Treatment is mainly based on the prevention of risk factors known to induce PTH oversuppression, such as aluminium and calcium load and very high doses of vitamin D receptor activators. Due to the limitations in the treatment of both conditions, prevention plays a key role in the management of these disorders.

Key words: *Adynamic bone, Bone fractures, Bone mass, CKD-MBD, Osteoporosis, Vascular calcification*

BONE AND VESSELS IN THE OLDER GENERAL AND CHRONIC KIDNEY DISEASE POPULATIONS

Bone problems have drawn the attention of nephrologists mainly in the area of renal osteodystrophy. However, for several reasons, of which the aging of the chronic kidney disease (CKD) population is the most relevant, other extremely frequent bone disorders such as osteoporosis have recently raised great concern (1). Other important reasons which explain the increased interest in osteoporosis are related to a better knowledge of the diagnosis and management of this disorder, together with the spread and improvement of the noninvasive techniques to assess bone mass as bone mineral density (BMD). Among them, dual-energy X-ray absorptiometry (DXA), considered the gold standard in this area, has played a key role (2). In addition, the recent development and marketing of new active drugs to treat osteoporosis has facilitated the fact that osteoporosis and bone fractures have become an important part of the chronic kidney disease–mineral bone disease (CKD-MBD) constellation (3). An additional contributing factor has been the long-term survival achieved in all forms of renal replacement therapies (RRTs), which has forced us to concentrate on other important areas such as the rehabilitation and quality of life of CKD patients. Bone tissue has excellent biomechanical properties; it possesses a great mechanical capacity to withstand tensile stress, which is lower than that of iron, but bone is at least 3 times lighter and 10 times more flexible (4). This outstanding property of bone explains why during long periods of life, mainly youth, only a reduced number of bone fractures occur despite the substantial number of falls suffered by many people.

Bone has such clinically relevant biomechanical properties thanks to the activity of the bone remodeling units, which allow the renewal of a mean of 5%-10% of the skeleton per year during young adult life. However, the capacity to renew

bone tissue slowly decrease after age 50, showing a progressive reduction with age (4).

The maximum value of bone mass, known as peak bone mass, is achieved around the age of 20, and it is influenced by several factors, some of them unmodifiable, such as the individual's sex and heredity. However, there are other important, modifiable factors such as nutrition, exercise and lifestyle that need to be taken into account (5).

It is well-known that an individual's sex influences the peak bone mass, and women achieve a lower peak bone mass than men. In addition, after the fifth decade of life, women also show a more rapid bone loss due to the well-known reduction in sex hormones. In addition to the previously mentioned sex- and age-dependent factors, other risk factors may have a relevant influence on the onset of osteoporosis and low bone turnover, both in the general and CKD populations – mainly in the advanced stages of CKD in the latter group (6).

Thus, when we analyze the role of osteoporosis in CKD-MBD, we have to take into account that on top of the bone disorders found in the general population older than 50 years, we have to add all of the specific abnormalities associated with the progression of CKD, particularly those factors related to the dysregulation of the calcium-phosphate-vitamin D-FGF 23-parathyroid hormone (PTH) axis. All of these CKD abnormalities, together with their clinical consequences, have been included in the new definition of the bone and mineral disorders associated with CKD (CKD-MBD) (7). In this scenario, aging plays a key role, and its effect is so powerful that it currently overcomes and masks most other factors which may influence bone metabolism in the general and CKD populations.

Among the CKD-MBD disorders strongly influenced by age, bone turnover, low bone mass and, consequently, bone fractures and vascular calcification are considered of great importance, as they represent a great public health problem. Furthermore, low bone turnover, bone osteoporotic fractures and vascular calcification have been independently associated with greater mortality, both in the general and CKD populations (8, 9). Several epidemiological, clinical and experimental studies have shown that apart from age, there are also some other possible reasons which may partly help us to understand why the most severe bone losses are associated with more rapid and severe vascular calcification (10-15). This occurs mainly in medium- and large-caliber arteries, and it has also been extensively studied in the coronary tree (16).

In fact, recent studies carried out in the general and CKD populations have found that after 4 and 2 years of follow-up, respectively, the progression of aortic calcification was

associated with greater bone loss and an increased incidence of bone fractures. Furthermore, the latter was associated with a significantly greater mortality in CKD stage 5 patients (9, 10). Confirming this association, other papers have shown that the magnitude and severity of coronary calcification were associated with low bone activity and low bone mineralization, even in patients not yet undergoing dialysis (16, 17).

In the general population, the bone disorder that has been more consistently associated with an increase in vascular calcification is osteoporosis; meanwhile, in CKD, both osteoporosis and low bone turnover, namely adynamic bone, are the predominant bone disorders associated with increased vascular calcification (12-20). Despite osteoporosis and adynamic bone sharing similar clinical consequences, such as a greater prevalence and severity of vascular calcification, both disorders have different pathophysiological backgrounds (19, 21), and consequently, different clinical management strategies are needed. Also the diagnosis and treatment of bone disorder and vascular calcifications in CKD remain controversial (7, 22, 23). In the following section of this review we will highlight and discuss the similarities and differences between osteoporosis and adynamic bone.

DEFINITION, PATHOPHYSIOLOGY AND MANAGEMENT OF OSTEOPOROSIS IN CKD

In osteoporosis, there is a reduction in bone mass with no specific defect in bone formation. This is due to the fact that the balance between bone formation and bone resorption is lost, favoring the latter. As a result, less new bone is formed to replace bone losses (24-26). When this condition is assessed by using the tetracycline-labeling technique for bone biopsy, the bone formation rate is found to be either low or normal. Nevertheless, in clinical practice, the diagnosis of osteoporosis is not based on the histological analysis, but on the measurement of BMD using DXA (25-27). Bone biopsies are rarely used to diagnose osteoporosis: for example, a large osteoporosis clinic was recorded as performing the procedure in 0.003% of patient consultations (28). However, when a bone biopsy is performed, it gives useful information regarding bone quality, bone turnover, degree of mineralization and safety of drugs (29).

The DXA definition of osteoporosis and the bone mass criteria followed for its diagnosis were adopted for the first time by the World Health Organization (WHO) in 1994 (27). It is defined as “a disease characterized by low bone mineral density and micro architectural deterioration leading to low bone strength and increased risk of fractures” (27).

Strictly speaking, the definition applied only to white postmenopausal women, and it was conceived of to be used for diagnostic but not treatment purposes. However, its use expanded progressively, being also applied to men, and it was adopted to help in the treatment decision process too. In any case, the WHO definition of osteoporosis has never included the CKD condition.

The WHO definition of osteoporosis has 2 clear and different components: The first is the BMD changes, which does not yield any information related to micro architectural changes. It is likely, though, that in the near future, new, sophisticated techniques such as quantitative micro-computed tomography (micro CT), high-resolution QCT and finite element analysis, so far not available for clinical practice, may help us to study, in the clinical setting, quality and micro architectural changes. The second component of the WHO definition of osteoporosis is the clinical consequence of having low bone mass and micro architectural deterioration, as represented by the bone fragility fracture, also called an osteoporotic fracture. By definition, this type of fracture occurs with no or low-energy trauma in any bone of the skeleton, excluding the skull or fingers, though the vertebrae, hip and wrist are the most common sites of osteoporotic fractures (25-27, 30, 31).

In the general population, epidemiological studies have claimed that BMD measurement may predict up to 70% of the fracture risk, and every standard deviation (SD) decrease in BMD doubles the fracture risk (30). The T-score is used for the evaluation of BMD and for the definition of the different stages of BMD according to the WHO definition of osteoporosis. Each T-score difference in BMD represents 1 SD from the peak bone mass. Values up to -1 SD BMD below the mean peak bone mass are considered normal; values between -1 SD BMD and -2.5 SD are indicative of osteopenia and values below -2.5 SD BMD are indicative of osteoporosis (27) (Fig. 1).

Even though a BMD <-2.5 SD is a good predictive risk factor for osteoporosis, the strongest risk factors predicting osteoporotic fractures are older age and the presence of a previous bone fragility fracture at any site (31-33). Therefore, using a widely available technique such as a spine X-ray evaluation to look for vertebral deformities plays a key role in the prevention and treatment of the population with high risk of osteoporosis. For this reason, the International Osteoporosis Foundation has recently launched a campaign called "Capture the Fracture" aiming to spread the use of spine X-ray to detect asymptomatic vertebral osteoporotic fractures, a simple and widely available strategy that can assist in the diagnosis and prevention of further bone fractures.

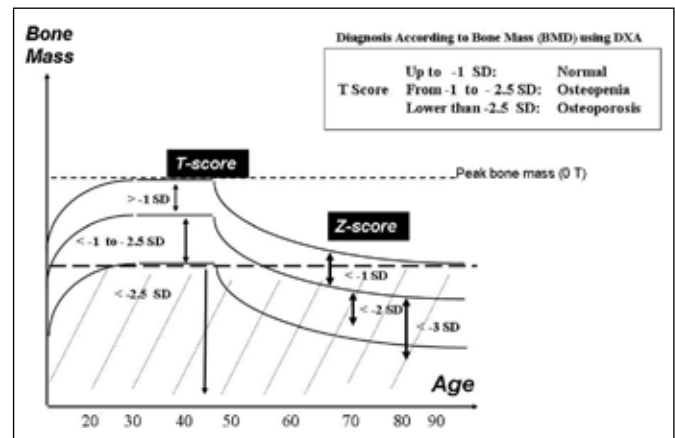


Fig. 1 - The WHO osteoporosis diagnostic criteria: T-score values for normality, osteopenia and osteoporosis. Z-score: comparisons with the same age (1 SD). DXA = dual-energy X-ray absorptiometry.

In addition to the T-score, which is the accepted criterion for a DXA diagnosis of osteoporosis in the normal population, another approach to analyzing BMD differences is to compare the BMD values among people of the same age and sex, as represented by the Z-score. The Z-score has proven to be particularly useful in children and CKD patients, in whom there are no normal reference values. Thus comparison with age- and sex-matched groups represents a useful approach to studying and evaluating bone mass in specific populations (1, 27, 34).

BMD measurement plays an important diagnostic, preventive and managerial role in the general population, but unfortunately, when it comes to CKD, this technique has a rather limited utility. The good correlation between BMD values and fractures observed in the general population does not apply to the CKD population; this limitation is even more noticeable in the more advanced stages of CKD (1).

The recently published Kidney Disease Improving Global Outcomes (KDIGO) guidelines address this topic (7). After evaluation of the few available cross-sectional studies which fulfilled the guidelines' inclusion criteria, the KDIGO board found only a weak relationship between BMD values and bone fractures, and they pointed to important additional limitations, such as the fact that only 1 skeletal site and a reduced number of patients were included in most of the studies (7). The reasons for the poor correlation between BMD and bone fractures in CKD patients have not been specifically studied; however, it is possible that a much higher prevalence of vascular calcification (9, 10) and arthritic lesions in CKD patients may partly account for this poor correlation. In addition, in renal osteodystrophy, the most important bone changes are related to the quality and

structure of bone, rather than to bone mass abnormalities, and since the former cannot be captured with DXA, a bone biopsy is required to adequately assess this aspect. Due to all of the previously discussed reasons, DXA has a rather limited value for the diagnosis of osteoporosis in CKD. Nevertheless, in certain scenarios, BMD measurement can give useful information related to the amount of bone mass. For this reason, it has been suggested to use BMD values to assess bone mass, only to find out whether a patient has high, normal or low bone mass, while stressing that there is no correlation between BMD values and bone turnover (1). Despite the fact that BMD measurement does not help in the specific diagnosis of the CKD-MBD disorders, it can be useful for monitoring BMD changes after the use of drugs known to influence bone mass, such as steroids, bisphosphonates and calcimimetics (35-37). BMD measurement is also particularly useful in the short-term bone follow-up of transplant patients (38). Thus BMD values cannot be used, as they are in the general population, as osteoporotic diagnostic criteria in CKD patients.

The prevalence of bone fragility fractures in CKD patients is greater than in the general population, but there are important differences between vertebral and nonvertebral (peripheral) fractures (39-41). In CKD stages 3-5, nonvertebral fragility fractures occur 2 to 6 times more frequently than in the general population, and they are more common in patients older than 50 years (40, 41). However, it is important to stress that in CKD stage 5 patients (i.e., those on dialysis), age is not as important as in the general population, because due to the more complex bone abnormalities found in CKD, almost half of those bone fractures occur in patients younger than 50 years. Defects and variations in the production of the mature osteoid influenced by the rate of bone turnover, such as woven bone, not captured by the BMD measurement, can change the bone quality and may partly explain the latter (42). In contrast with the results observed in nonvertebral fractures, there are fewer differences in the prevalence of vertebral fractures between normal and CKD populations (25). A study comparing both types of fractures in people of the same age and from the same geographical area revealed no relevant differences in the prevalence of vertebral fractures in women and men older than 50 years (39, 40) (Fig. 2). The prevalence and incidence of asymptomatic vertebral fractures are currently underestimated in the general and CKD population. In addition, as has been shown in the COSMOS study, in European countries there are important differences in the frequency and routine use of spine X-ray in CKD patients (43). Lateral DXA with vertebral morphometry has also been successfully used to assess vertebral fractures in CKD patients (44), but this technique is restricted to a few specialized centers.

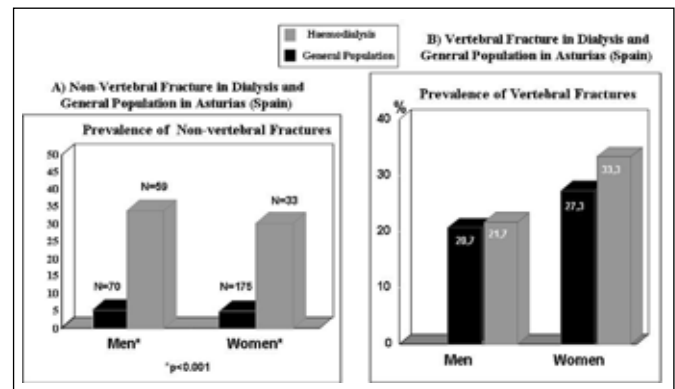


Fig. 2 - Nonvertebral (A) and vertebral (B) fracture prevalence in dialysis and general populations in Asturias (Spain). Modified from our own data (39, 40).

The most likely explanation for the important differences in the prevalence of vertebral and nonvertebral fractures is most probably related to the long-term effects of secondary hyperparathyroidism on the cortical bone, which favor a greater porosity, reduce the cortical thickness and increase the cortical weakness. Unfortunately, the deleterious long-term effects of high PTH levels on bone cortex structure cannot be evaluated with a single measurement of the serum PTH level at the time of the bone fracture. One isolated serum PTH value cannot capture the long-term and sustained effect of several years of high PTH levels on bone. In general terms, CKD patients in stages 1, 2 and 3A [creatinine clearance (CrCl) >45 ml/min] who do not show any important biochemical abnormalities can be diagnosed and managed in the same way as patients from the general population. In contrast, CKD patients in stages 3B (Cr CL <45 ml/min) and 4-5 should be individually evaluated and managed differently (7).

In addition to the aforementioned limitations to the interpretation of BMD, restrictions in the treatment of osteoporosis have to be taken into account in CKD patients. Apart from the specific use of calcium supplements and vitamin D receptor (VDR) activators in CKD due to the complexity of CKD-MBD, there are also important limitations in the use of the currently available antiosteoporotic compounds. Even though we do have a large number of active antiosteoporotic drugs, their use in CKD patients is quite limited. There are 2 main reasons for these limitations: First is the fact that all large-scale, long-term clinical trials carried out to register the active antiosteoporotic drugs have specifically excluded patients with low renal function, particularly those with estimated glomerular filtration rates lower than 30 ml/min, and second is the fact that kidneys play a key role in the clearance of some of these compounds (e.g., bisphosphonates

and strontium ranelate). Thus the available evidence comes from the post hoc analysis of the studies, selecting patients with reduced renal function in whom the drug was administered (45-53). In some of these studies, there were enough CKD stage 3 patients to extrapolate the results, but in others, that is not the case. Furthermore, this limitation is greater in CKD stage 4-5 patients (54). Therefore, knowledge of the effectiveness and safety of antiosteoporotic drugs is still limited. To fill that gap, recent studies have started to address this issue, such as a recent pilot, single-dose study performed with denosumab in patients with different degrees of renal impairment (55). It would be advisable that in the future, pivotal large trials for the registration of new antiosteoporotic agents specifically include patients with reduced renal function who require the progressive use of these drugs to manage CKD-MBD (54).

Despite the mentioned limitations, the KDIGO CKD-MBD guidelines reviewed this field and include the following advice: CKD stage 1-2 patients should be managed as the general population is (7). CKD stage 3 patients should be individually evaluated taking into account other important biochemical parameters such as PTH values. Patients with PTH within the normal range should be managed as the general population is. However, as CKD stage 3 comprises a rather heterogeneous group with glomerular filtration rates ranging from 60 to 30 ml/min, in this group it is necessary to monitor the progression of renal failure (54). Patients with biochemical anomalies, such as PTH or other serum bone parameter abnormalities, should be managed differently, and the treatment choices should take into account the magnitude and reversibility of those biochemical abnormalities; in addition, it is particularly important to carefully watch the progression of CKD. A bone biopsy should be always considered for this type of patient, and even greater caution is needed when considering the use of antiresorptive agents when PTH levels are low (7, 54).

Finally, in CKD stage 4-5 patients who have biochemical abnormalities or fragility fractures, additional investigations such as a bone biopsy prior to therapy with antiresorptive drugs are always advised. In this group, it is extremely important to carefully balance the risks and benefits of antiresorptive agents, and great caution must be exercised if low PTH levels are present (7).

PATHOPHYSIOLOGY AND MANAGEMENT OF ADYNAMIC BONE IN CKD

Adynamic bone is currently suspected based on the results of biochemical parameters, mainly PTH and bone alkaline phosphatase, but it needs to be proven using a bone bi-

opsy (56-58). Despite the fact that PTH levels lower than 150 pg/mL have a good predictive value for low bone turnover and adynamic bone, PTH values between 150 and 450 pg/mL, which are currently considered to be within the normal range, are also frequently associated with adynamic bone (59). Therefore, despite PTH level measurement being the main biochemical method used to evaluate bone turnover and, indirectly, adynamic bone in CKD, its specificity within the mentioned ranges is rather limited.

For the diagnosis of adynamic bone, it is necessary to perform a bone biopsy. The presence of a low rate of, or no, bone formation, the reduction or absence of osteoblasts and osteoclasts, together with the presence of low serum PTH levels and/or signs of low PTH activity are required to make the diagnosis (56-58).

The prevalence of low bone turnover and adynamic bone has greatly increased during the last 3 decades. Aluminum toxicity, calcium load and the use of extremely high doses of VDR activators have been the main factors responsible for PTH oversuppression in CKD. More recently, the progressive increment in the number of diabetics and older CKD patients, together with the still frequent high calcium load, have become the most important factors responsible for the high prevalence of low bone turnover states. Even though the cause of low bone turnover in diabetic patients seems to involve several factors (56-58), it has recently been suggested that sclerostin, a physiological inhibitor of bone formation secreted by the osteocytes, may be also involved (60), and increments in the serum levels of this protein have been observed in diabetic patients. In addition, serum sclerostin has been found to be a predictive factor for BMD but it is also an independent predictive risk factor for bone fractures (61).

A good demonstration of the changes occurred in the pattern of renal osteodystrophy comes from the analysis of a series of bone biopsies carried out throughout the last 30 years. In the early 1990s (62), histologically proven low bone turnover represented around 25% of the cases of renal osteodystrophy, whereas in more recent series, it has represented up to 60%-70% of cases in CKD stage 5D patients (63). Also in the CKD population not yet on dialysis, an increase in the prevalence of adynamic forms of bone turnover have been observed, but in CKD stages 2-4, the prevalence is much more limited, and the figures still vary depending on the geographical area. As an example, in one European study carried out in patients not yet on dialysis, low bone turnover forms represented 35% of the histologically proven cases of renal osteodystrophy (64); by contrast, in a recent South American series, the prevalence was close to 80% (17). Differences in age, genetics, envi-

ronmental factors, calcium load and nutrition may account for some of these differences.

Overall, the clinical consequences of low bone turnover observed in adynamic bone are similar to those observed in osteoporosis, with a higher prevalence of bone fractures and more frequent and severe vascular calcification compared with patients in whom bone turnover remains close to normal. A higher risk of mortality has also been associated with low bone turnover (65, 66).

The clinical management of adynamic bone also has important limitations and currently does not allow for the taking of many active measures (56-58). Treatment is mainly based on the prevention of those risk factors known to induce, facilitate or increase the progression of low bone activity. In general terms, the first step should be to rule out aluminum overload (56), and if there is any doubt about this possibility, a more complete study will be needed; also any pertinent measures to prevent aluminum exposure should be taken. The second step is to limit and/or reduce as much as possible all causes of PTH oversuppression, such as calcium load, either through the use of calcium-based phosphate binders or high calcium concentration in the dialysate (>1.25 mmol [2.5 mEq/L]) avoiding high doses of VDR activators. The previously mentioned factors, well-known causes of low bone turnover, are still frequent in some countries; thus a careful and individualized evaluation needs to be carried out to minimize them (56-58). In addition, other important aspects need to be taken into account, particularly those related to nutritional status, avoiding low-protein diets and excessive phosphate restriction, mainly in the elderly.

In summary, osteoporosis and adynamic bone states are 2 highly prevalent conditions in CKD patients. They can be present together, and both diagnoses are associated with negative outcomes such as bone fractures and more severe vascular calcification, which in turn have been independently associated with higher mortality rates. Due to the limitations in the treatment of both conditions, prevention still plays a key role in the management of these disorders.

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