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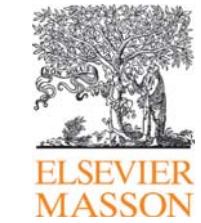

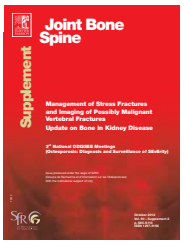

Osteoporosis: Chronic Kidney Disease in Rheumatology Practice

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1. Introduction

The annual incidence of chronic renal failure, now usually called Chronic Kidney disease (CKD), has been estimated in France at 1/1000 population [1]. Nephrology experts recently developed updated recommendations that take into account the risk of bone disease associated with CKD (Kidney Disease: Improving Global Outcomes [KDIGO], 2009) [2]. CKD is classified into five stages depending on the glomerular filtration rate (GFR) (Table 1). Osteoporosis is another common disease and occurs predominantly in the growing older age group [3]. As a result, an increasingly common task for rheumatologists is to manage osteoporosis and fracture risk in patients at various stages. of CKD.

CKD has a dual impact on the management of osteoporosis. First, a number of osteoporosis medications may worsen kidney failure or promote the development of vascular calcifications which contribute substantially to the morbidity and mortality of CKD. Second, CKD can induce specific bone abnormalities, which may affect the efficacy or safety of osteoporosis medications.

Here, after a brief review of epidemiological data, we discuss the specific aspects of fracture risk evaluation and management in patients with CKD.

Table 1
Chronic Kidney Disease stages in the KDIGO classification scheme [2].

Classification		
Stage	**Description**	**GFR (mL/min/1.73 m²)**
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild GFR decrease	60-89
3	Moderate GFR decrease	30-59
4	Severe GFR decrease	15-29
5	Terminal Kidney failure	<15 or dialysis

2. Epidemiology

2.1. *Prevalence of chronic kidney disease in patients with osteoporosis*

About 50% of patients with osteoporosis have stage 2/3 CKD, as demonstrated by post hoc analyses of data from efficacy trials of osteoporosis medications. In the pivotal efficacy trial of risedronate, 44% of the 9,887 patients had stage 2 CKD, 40%

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stage 3, and 6% stage 4 [4]. In the Fracture Intervention Trial, 9% of the 6,459 women had GFR values lower than 45 mL/min [5]. Finally, in the Multiple Outcomes of Raloxifene Evaluation, GFR values were greater than 60 mL/min in 32% of women, between 45 and 59 mL/min in 47%, and lower than 45 mL/min in 21% [6].

2.2. Prevalence of osteoporosis in chronic kidney disease

Osteoporosis is also highly prevalent among patients with CKD. In 13,500 individuals from the NHANES III cohort, associations between bone mineral density (BMD) and renal function were evaluated. After adjustment on age, sex, and body weight, CKD was not associated with femoral-neck BMD. However, in an older subgroup (50-74 years), CKD was 3 times more prevalent among individuals with a history of hip fracture than in other individuals [7]. This finding suggests that CKD may be an independent risk factor for bone frailty. Confining the analyses to the 7,120 women in the NHANES III cohort showed that 23.8% of women with osteoporosis had creatinine clearance values lower than 35 mL/min and that 61.3% of women with BMD values in the osteoporosis range had creatinine clearance values between 35 and 60 mL/min [8]. These results are evidence of a strong association between CKD and osteoporosis. Clearly, rheumatologists should monitor renal function in their patients, and nephrologists must measure BMD in theirs.

3. Bone disease related to chronic kidney disease

3.1. Nosology

Every patient with CKD is at risk for developing osteoporosis, that is, a decrease in bone strength associated with an increased risk of fractures. However, when seeking to minimize the risk of bone disease in patients with CKD, a major challenge is that bone loss (or a decrease in bone mass) may be combined with disorders in bone mineralization and/or turnover. This spectrum of abnormalities was previously designated "renal osteodystrophy", a term now reserved for the histological bone abnormalities seen in CKD [2]. The set of clinical manifestations (fractures, vascular calcifications, and mortality) and abnormalities in calcium and phosphorus homeostasis associated with CKD is now called "CKD-mineral and bone disorder" (CKD-MBD). CKD-MBD can develop starting at CKD stage 3. The clinical presentations of bone histological lesions of CKD-MBD include *osteomalacia* (a disorder of bone mineralization); *osteitis fibrosa* (characterized by a high turnover, usually related to secondary hyperparathyroidism); *mixed bone disease*, defined as a combination of osteomalacia and osteitis fibrosa; and *adynamic bone disease*, characterized by a very low bone turnover. Each of these presentations may affect bone mass and the degree of secondary mineralization (Fig. 1), both of which determine bone strength.

3.2. Characterization of the CKD-BMD pattern in everyday practice

This is a crucial step in bone risk management in patients with CKD. CKD-MBD can contributes to decreased bone strength and requires treatment adjustments that are specific of each pattern of bone disorder. In addition, a number of osteoporosis medications may exacerbate CKD-MBD.

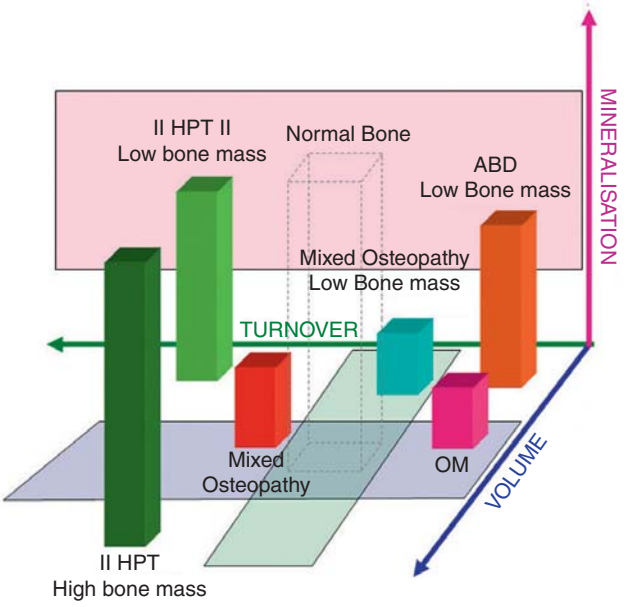

Figure 1. TMV classification system for bone histomorphometry (from [24]).

The figure is a graphical example of how the TMV system provides more information than the present, commonly used classification scheme. Each axis represents one of the descriptors in the TMV classification: T, turnover (from low to high), M, mineralization (from normal to abnormal), and bone V, volume (from low to high). The bars represent normal ranges and the gray parallelepiped normal bone. Individual patient parameters can be plotted on the graph, or means and ranges of grouped data can be shown. For example, many patients with CKD-MBD cluster in the areas shown by the bars. The deep pink bar (OM, osteomalacia) is currently described as low-turnover bone with abnormal mineralization. Bone volume may be low to high, depending on the severity and duration of the process and other factors that affect bone. The orange bar represents adynamic bone disease (ABD). It is currently described as low-turnover bone with normal mineralization, and the bone volume in this example is at the lower end of the spectrum, whereas other patients may have normal bone volume. The green bars on the left represent secondary hyperparathyroidism -II HPT) with low and high bone mass, respectively. The red and blue bars represent mixed uremic osteopathy (MUO) with high and low bone mass, respectively. This diagram represents distinct categories, but a range of abnormalities exists along a continuum from medium to high turnover and bone volume can have any value, depending on the duration of the disease process. In summary, the TMV classification system more precisely describes the range of abnormalities that can occur in patients with CKD.

A low turnover rate indicates adynamic osteopathy. Low bone turnover with mineralization disorders and no increase in bone resorption is consistent with pure osteomalacia. A high turnover rate suggests either osteitis fibrosa or, in the presence of osteomalacia, mixed bone disease.

Assays of serum bone alkaline phosphatase (BAP) and parathyroid hormone (PTH) provide information on bone turnover and can differentiate lesions of secondary hyperparathyroidism from those of adynamic osteopathy in about 80% of cases [9]. In patients with advanced CKD, BAP and PTH should, if possible, be monitored over about 6 months, as substantial variations may occur.

However, bone marker assays seem unable to predict bone mineralization disorders such as osteomalacia, particularly in patients with secondary hyperparathyroidism responsible for mixed bone disease. Bone marker data should therefore be