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IN FOCUS

Skeletal fractures in patients on renal replacement therapy: how large still is the knowledge gap?

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Skeletal fractures represent the main negative outcome of most bone diseases. In fact, in the general population the principal parameter for judging the efficacy of therapies directed to correct a bone disease is based on their efficacy in preventing the occurrence of fractures and the consequent disability, as is the case of osteoporosis.

It is also well recognized that bone involvement occurs almost invariably in CKD patients, in particular in the more advanced stages, and even after renal transplantation this complication remains a main problem. However, although a wealth of studies are published yearly in the CKD-mineral bone disorder (MBD) field, only scanty data deal with the risk of fractures in the different stages of CKD and even less with the efficacy of the therapies used for controlling mineral metabolism (MM) and bone-related parameters on this primary clinical complication.

This is disappointing, given that most of the few observational studies published on this topic clearly show that the fracture risk is manifoldly higher in CKD and renal transplant patients as compared with matched normal subjects [1–4]. A recent study stressed this concept, showing that the incidence of fractures progressively increases with the lowering of GFR from the early stages of CKD [5]. Furthermore, the fracture risk has been reported to be increased in patients who experienced an acute kidney injury (AKI) necessitating dialysis, even when an almost complete recovery of renal function occurs [6].

The shortage of information on this argument is even more daunting in view of the fact that the occurrence of a fracture event is associated with a consistently increased risk of death in both dialysis and renal transplant patients [7–11].

On these considerations, any additional information on this topic is very welcome.

In this issue of *Nephrology Dialysis Transplantation*, Hensen *et al.* [12], based on data from the Danish Nephrology Registry, report on the fracture risk of CKD patients who were on dialysis on 1 of January 2000 or started dialysis between January 2000 and December 2011 inclusive, and of all patients who received a renal transplant during the same period of time. The dialysis and renal transplant patients were compared with the general Danish population >18 years of age as of 1 January 2000. For all the patients and health subjects, the occurrence of a first fracture event was recorded based on the data available in the National Patient Registry, which contains data on events and treatments of both inpatients and outpatients, so that almost all types of fractures are recorded, in contrast with most previous studies, which reported only on hip and other major fractures.

The first finding was that dialysis and renal transplant patients have a 3-fold and 2-fold risk of fractures, respectively, as compared with healthy subjects. This difference was maintained even after adjustment for the main personal and clinical covariates (age, gender, comorbidities, time on dialysis, etc.). It is worth noting that the reported rate of fractures was consistently lower than those reported in older studies [1–4, 13] and closer to the fracture rate reported in the recent data from the Dialysis Outcomes and Practice Patterns Study, at least as far as the data referring to the hip fracture rate observed in the Swedish population are concerned [10]. The discrepancy between the data of more recent studies and those of older ones cannot be attributed to an underreporting of fractures in the former, because, as previously underlined, this possibility would have had an effect on the latter studies. It cannot be excluded, however, that differences in the ethnic and/or comorbidity characteristics of different cohorts could explain part of these different results. Another potential explanation may be linked to improvements in the therapeutic tools for the control of CKD-MBD. This hypothesis could be indirectly suggested by some recent studies that showed a trend in a reduction of fracture rates in both dialysis [14] and transplanted patients [15] during the first decade of the present century. However, at odds with these studies, the data presented by Hensen *et al.* in this issue seem to contradict such a hypothesis. In fact, when three different time periods were compared (2000–2003, 2004–2007, 2008–2011), the fracture rate remained completely unchanged in both dialysis and renal transplant patients. These conflicting results raise some old and never answered questions. First, are the available therapies to correct MM parameters also effective on fractures in CKD patients? In the primary analysis of the results of the most important study carried out on this topic [16], we realized that, although the more recent therapeutic tools have been shown to be effective in the control of MM parameters, this did not translate into any apparent improvement of fracture occurrence in dialysis patients. Strictly linked to this question is a second one: are the MM derangements the true culprits of fractures in CKD? In fact, evidence that MM parameters play a major causal role in such a clinical complication is scanty and controversial. Some data seem to suggest that, at least in renal transplant patients, higher PTH levels might be associated with an increased fracture risk [17]. On the other hand, the studies dealing with the relationship between MM parameters and the occurrence of fractures in dialysis patients reported only marginal or no role for PTH and no effect at all for calcium and phosphorus on the fracture risk [18, 19]. Some studies even reported that low, more than high, PTH levels were associated with an increased risk of fractures [13, 20]. These data suggest that when we approach the problem of fracture prevention in CKD, we should take into account other causal factors, as for the prevention of osteoporotic fractures in the general population, not strictly related to the MM parameters that are considered the classic targets of our medical intervention [21]. As yet, we have scanty and largely undefined notions of what might be the role in CKD patients of drugs already in use, or proposed to be used, in the general population for preventing the occurrence of fractures, such as bisphosphonates, denosumab, or anti-sclerostin antibodies [21–24].

Missing information common to most published studies dealing with fracture topics in CKD, including the study from Hensen *et al.* in this issue, is related to the underdiagnosis of 'asymptomatic' vertebral fractures. In fact, this type of fracture can be detected only if a systematic radiological assessment of the thoracic and lumbar spine is performed in each patient according to well-defined criteria [25, 26]. Since these fractures are usually asymptomatic, more than two-thirds of them remain undiagnosed [27]. However, in our personal data set of CKD patients explored for asymptomatic vertebral fractures at the time of renal transplantation, >25% had at least one fracture in one or more thoracic and/or lumbar vertebrae, with this figure being completely similar to that reported in another study [17].

Missing diagnoses of these fractures is of relevance since it has been demonstrated that asymptomatic vertebral fractures are associated not only with a greater risk of developing future, more severe (symptomatic) vertebral fractures, but also with fracture events in other skeletal sites, an increased risk of physical and psychological disability, and of morbidity and death [21, 27].

Summarizing, the paper of Hensen *et al.* confirms that the incidence of fractures is higher in CKD patients on renal replacement therapy.

The community of nephrologists involved in clinical research related to CKD-MBD should devote much more effort to gaining insights into the following issues:

- To know more precisely the present prevalence and incidence of fractures in the different CKD cohorts
- To assess CKD patients for the presence of 'asymptomatic' vertebral fractures
- To clarify if and how much MM changes are really involved in the pathogenesis of skeletal fractures
- To define if, in CKD patients, there is a place for the use of drugs already used or proposed to be used in the near future for fracture prevention in the general population.

Thus we look forward to receiving not only observational data, but hopefully new randomized controlled trials on these topics.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Hansen *et al.* Risk of fracture in adults on renal replacement therapy: a Danish national cohort study. *Nephrol Dial Transplant* 2016; 31: 1654–1662)

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Cum grano salis

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In this issue of *Nephrology, Dialysis and Transplantation*, Ayus *et al.* [1] report on the association between chronic hyponatraemia and the risk of hip fracture in an elderly population. The authors use a retrospective analysis of data derived from a health maintenance organization administrative database. The study includes 31 527 adults, whereby 'elderly' is defined as age >60 years and chronic hyponatraemia as two consecutive measurements of serum sodium <135 mmol/L. Elderly patients with chronic hyponatraemia had a 4.5 times higher relative risk for hip fracture.

Whereas this result seems impressive, and is in line with previous reports describing an association between chronic