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Received for publication: 26.4.07
Accepted in revised form: 6.7.07

Nephrol Dial Transplant (2007) 22: 3377–3380
doi:10.1093/ndt/gfm508

Towards the prevention of bone fractures in dialysed patients?

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Keywords: epidemiology; fall; fracture; hemodialysis; prevention

Epidemiology of bone fractures in dialysed patients

Incidence

Alem *et al*. [1] have compared the incidence of hip fractures in US dialysis patients [based on United States Renal Data System (USRDS) Registry data] with that of the general population, based on data from Olmstead County (Minnesota). They report a four times higher incidence in dialysed patients matched for age, gender and race (the study being limited to Caucasians).

Very recently, the incidence of hip fractures and all fractures has been studied in the 12 countries of the Dialysis Outcomes and Practice Patterns Study (DOPPS, phase 2). The yearly incidence is 0.89% for hip fractures and 2.6% for all fractures (for a mean age around 60 years), without major differences between countries after adjustment for demographics and comorbidity [2]. This study extends to the worldwide haemodialysis (HD) community the evidence of a much higher incidence of hip fracture in HD patients than in the general population. Indeed, at around 60–65 years, the yearly incidence ranges from 0.07% to 0.22% in the general population (reviewed in [16]), *vs* 0.49–1.57% in HD patients from DOPPS 2 countries (Table 1). The incidence of hip fractures in HD patients is actually similar to or higher than that of the general population aged 10 to 20 more years! The reasons for this much higher incidence in HD patients are discussed below.

Risk factors

Stehman-Breen *et al*. [3] identified multiple independent risk factors for hip fracture in dialysed

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Table 1. Yearly incidence of hip fracture

Reference	Country	HD	General population with similar age
1	USA	1%	0.22%
2	12 DOPPS two countries	0.89% 0.47–1.57%	0.07–0.22%*

*References available in [2].

patients: older age, female gender, low body mass index, Caucasian race and peripheral vascular disease. These findings confirm in dialysed patients many known risk factors for osteoporosis and/or hip fractures in the general population. Strikingly, these authors were unable to detect any role for mineral metabolism parameters (including the serum levels of calcium, phosphorus, parathyroid hormone (PTH), bicarbonate and aluminium) [3]. More recently, Ball *et al*. [4] showed that the risk of hip fracture was increased not only within the first 3 years after kidney transplantation (most likely as a result of the treatment by steroids) but also with increasing dialysis vintage. The analysis of DOPPS data confirms the independent role played by the above-mentioned risk factors [2].

In addition, a markedly elevated PTH level (>900 pg/ml) was also an independent risk factor for any fracture in DOPPS [2]. Several recent studies thus concur in incriminating severe hyperparathyroidism as an important factor in the genesis of fractures in HD patients. Danese *et al*. [5], analyzing waves 1, 3 and 4 of the DMMS study, found a PTH level exceeding 300 pg/ml to be an independent risk factor for fracture. Block *et al*. [6] analysed the Fresenius Medical Care database and detected a significant, albeit moderate, direct correlation between PTH level and the risk of fracture. In contrast, Coco and Rush [7] detected an association between PTH level below 195 pg/ml and an increased risk of fracture, a finding that requires confirmation. The recent *post hoc* analysis of all randomized controlled trials of cinacalcet *vs* placebo (in both arms with standard treatment of hyperparathyroidism) further shows a significantly lower actuarial risk of fracture in the cinacalcet group [8]. This *post hoc* analysis requires confirmation by randomized trials, including fractures in the pre-defined major endpoints.

More importantly, the database of drug treatment in DOPPS 2 was used to assess the potential role of several classes of medications. Using Cox proportional hazards regression, the use of several classes of psychoactive medications was independently associated with an increased risk of either any fracture or of hip fracture. These classes include selective serotonin reuptake inhibitors (SSRI) anti-depressants, benzodiazepines and narcotics [2]. Residual confounding may account for the fact that the risk of fracture was independently associated with SSRI anti-depressants but not significantly so with tricyclics anti-depressants.

As recent observational studies in the general population suggest that statins and β-blockers may protect from bone fractures, the DOPPS database was analysed in that respect but the analysis failed to detect any significant association in HD patients [2].

Prognostic impact and costs

After adjustment for the associated comorbid conditions, the onset of a hip fracture in a HD patient is associated with more than doubling of the death risk (reaching 50%) within a year. Not surprisingly, the costs associated with a fracture are high: for a US HD patient in 2004, they averaged 20 800, 17 000 and 14 500 dollars for a hip, vertebral or pelvic fracture, respectively [5].

Why is the fracture risk increased in HD patients?

Two main mechanisms may account for the increased fracture risk in HD patients: either a lower resistance of bone after relatively minor traumas or an increased propensity to falls.

Numerous factors may account for a lower resistance of bone in HD patients. These include, as discussed above, severe hyperparathyroidism and/or other components of the complex renal osteodystrophy. The potential role of a reduction of bone density (analogous to post-menopausal osteoporosis) is discussed below. It should be pointed out that no study has looked so far after possible associations between the incidence of bone fractures and bone histomorphometric analyses in dialysed patients. The β-2 microglobulin amyloidosis may also contribute to bone fractures, especially at the femoral neck level. Finally, two prospective observational studies in the general population in the US and the Netherlands have recently demonstrated an increased risk of fracture, either of hip or of hip and wrist, respectively, in subjects with hyperhomocysteinaemia, despite adjustment for many confounders (including age, gender, creatinine serum level, bone density, etc.) [9,10]. Hyperhomocysteinaemia might inhibit cross-linking of bone collagen. The role of hyperhomocysteinaemia is further supported by a recent randomized trial demonstrating a four times lower risk of hip fracture in hemiplegic patients randomized to folate and B vitamins than to placebo [11]. Still, the *post hoc* analysis of a recent, large-sized, randomized trial of the impact of B vitamins and folic acid on the risk of clinical cardiovascular events failed to show a reduction of the risk of fracture [12].

An increased propensity to falling is the other mechanism that may account for an increased fracture risk. Studies in the general population have indeed shown that the risk of hip fracture is more tightly associated with risk factors for falling than with risk factors of osteoporosis or with bone density [13].

Surprisingly, until recently, no data was available concerning the incidence and risk factors for falling

in HD patients, despite the marked increase of the average age of HD patients over the last two decades. Desmet *et al*. [14] thus studied prospectively the incidence of any fall (even minor) in 308 HD patients from eight Belgian units. At baseline, potential risk factors for falling (including demographics, biochemical parameters, drug treatment and some comorbidities) were recorded. The nursing staff of each unit then interviewed at least weekly all participating patients concerning the onset of falls. Over the 8 consecutive weeks of the study, 39 patients fell at least once for a total of 56 falls, a yearly incidence of 1.18 falls/patient-year. One-third of these falls caused lesions requiring health care (or even hospitalization in six cases). By logistic regression, risk factors for falling included older age, diabetes, the intake of any antidepressant, the total number of drugs and failing to walk without help for 10 metres. Diabetes may favour falls due to neuropathy (either peripheral or autonomic), retinopathy and/or peripheral vascular disease. The role of psycho-active agents such as antidepressants is in line with the DOPPS results concerning fractures [2]. Very recently, Cook *et al*. [15] followed prospectively for $\geq$1 year 162 HD patients aged $\geq$65 years. The incidence of falls was 1.6/patient-year. Risk factors for falling included older age, higher comorbidity, lower mean pre-dialysis systolic blood pressure and a history of falls [15]. Overall, both studies emphasize in HD patients the risk associated with several classical 'geriatric' risk factors for falling. In addition, despite the absence of control group of similar age but not undergoing maintenance dialysis, they strongly suggest that after matching for age and gender, the incidence of falls in HD patients is roughly twice as high as in the general population [14–16], probably a major contributor to the higher incidence of hip fractures in HD patients.

Is there a place for measuring bone density and treating osteoporosis in HD patients?

Extrapolating to HD patients the evidence-based medicine of screening for and treating postmenopausal [17] osteoporosis may be at least premature. Firstly, there is concern that hip or spine density results may be misleading in chronic kidney disease patients [18]; secondly it is true that the risk factors for a reduced bone density include, in dialysed patients, older age, female gender, white rather than black race, a history of kidney transplantation or premature amenorrhoea and that bone density is inversely correlated with PTH level and directly with a history of parathyroidectomy (reviewed in [16]). Still, in contrast to post-menopausal osteoporosis, studies looking at associations between fractures and bone density in HD patients rely on a history of fracture: no prospective study has demonstrated in dialysed patients that a reduced bone density predicts a higher risk of subsequent fracture [19].

More importantly, none of the 'evidence-based' drug treatments for post-menopausal osteoporosis has as yet been shown to improve bone density or safely reduce fracture risk in HD patients.

The available data regarding the efficacy and safety of bisphosphonates in dialysed patients remain very limited. Wetmore *et al*. [20] randomly assigned 31 HD patients to alendronate, 40 mg once a week for 6 weeks, or placebo. After 6 months, a marginal improvement of bone density was observed at Ward's triangle (but not at femoral neck or lumbar spine), as compared with placebo. In view of the risk of an excessive reduction of bone turnover and of the very limited information regarding the safety of bisphosphonates in dialysed patients, clinicians considering the use of these drugs in HD patients should carefully weigh the pros and cons and probably limit their use to patients with vertebral fractures and severe osteoporosis, awaiting the results of additional studies.

Hormone replacement therapy has recently been shown, in a large randomized controlled trial in post-menopausal women without known CKD, to be associated with a significantly increased risk of stroke (a secondary endpoint) and should thus probably be used very cautiously, if at all, in the post-menopausal HD population at high cardiovascular risk [21].

The prescription of raloxifen, a selective oestrogen-receptor modulator, was recently associated in a placebo-controlled study with a moderate increase of trabecular but not cortical bone in 16 HD patients treated for 1 year [22] and was well tolerated. Caution is warranted here too, especially as a long-term controlled trial of raloxifen in the general population demonstrated a reduction of vertebral fractures but an increased risk of fatal stroke [23].

Finally, no clinical study has been published hitherto concerning the potential use in the treatment of osteoporosis in dialysed patients, of recombinant PTH, strontium, calcitonin or denosumab, a monoclonal antibody to the receptor activator of nuclear factor κB (RANK) ligand [24].

Potential strategies to prevent fractures in dialysed patients

Three strategies, not mutually exclusive, may help reduce the burden of fractures in dialysed patients (Table 2).

Table 2. Potential strategies to reduce the risk of fractures in HD patients

1. Optimize the management of mineral metabolism, including PTH level, throughout the course of CKD.
2. Apply fall prevention strategies:
   - review and if possible reduce psychoactive medications, especially benzodiazepines, anti-depressants and narcotics;
   - refer for strength, gait and balance testing, followed by targeted training;
   - encourage progressive exercise training;
   - assess vision and environmental risks.
3. Consider the use of hip protectors in high-risk patients.

Firstly, the optimal management of mineral metabolism parameters, including PTH level, throughout the course of chronic kidney disease (a broad topic, beyond the scope of this contribution) should help.

Secondly, randomized controlled trials have provided an evidence base for the prevention of falls in elderly non-uraemic subjects [25]. The most effective interventions are multitargeted and usually include a careful review of the risks of all medications, especially psychoactive medications such as benzodiazepines, narcotics and anti-depressants. A second intervention is evaluation of strength, gait and balance testing, followed by targeted training. Some large-sized studies have demonstrated a subsequent reduction of fracture risk exceeding 60% [25]. Other interventions include visual assessment (with cataract surgery if appropriate) and assessment for environmental risk factors for falling. The available observational data on risk factors for falling in HD patients suggest that such interventions may help prevent fractures in HD patients too.

Finally, the use of hip protectors has been shown to reduce the risk of hip fracture in high-risk subjects such as nursing home residents [26]. This may again probably be extrapolated to the now delineated subgroup of HD patients at high risk of hip fracture [2,3].

Conflict of interest statement. The author has received research grants and honoraria from Amgen, the company marketing cinacalcet.

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Received for publication: 11.9.06
Accepted in revised form: 2.7.07