Hot topic in geriatric medicine

Management of the oldest old with osteoporosis

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ABSTRACT

The incidence of osteoporotic fracture increases with age; the median age for hip fracture, the most serious manifestation of osteoporosis is approximately 83 years. Osteoporotic fracture risk is multifactorial, and is determined by the balance between bone strength and the propensity for falling. Frailty is an independent predictor of falls, hip fractures, hospitalisation, disability and death in the elderly that guides for clinical decision-making, and may emerge as a therapeutic target. Non-pharmacological strategies to reduce fall risk can contribute to prevent osteoporotic fractures. Weight-bearing exercise and balance training programmes are recommended. Nutrition, particularly dietary proteins are of importance in preventing falls and fracture, as well as in fracture rehabilitation. Vitamin D and calcium supplementation is effective in reducing both falls and osteoporotic fractures, including hip fractures. Specific efficacious anti-osteoporosis drugs are underused. The evidence base for the efficacy of most such drugs in the very elderly is incomplete, particularly with regard to nonvertebral and hip fractures. Nonadherence to treatment is a substantial problem, which precludes efficacious therapeutic regimens to fulfill their goals.

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1. Introduction

The lifetime risk of experiencing a fracture since the age of 50 is 51% in women and 20% in men [1]. The incidence of vertebral and especially hip fractures increases steeply with age [2]. Hip fractures are generally regarded as the most serious manifestation of osteoporosis, associated with substantial morbidity and mortality [3–5]. Over 90% of hip fractures require surgical treatment. The incidence of hip fracture increases exponentially with age in women between 60 and approximately 85 years [4,6], beyond which it increases more slowly. Hence, 60% of hip fractures in women occur after the age of 80 years, and the median age for hip fractures in women is approximately 83 years [7]. Up to 40% of hip fractures concern patients living in nursing homes [4]. This is probably related to advanced age and to a high prevalence of comorbidities requiring long-term care. Moreover, this population is at high risk of recurrent falls. Mortality after hip fracture is higher in the general male population, with a life expectancy approximately 7 years shorter than unfractured. Given the reduction of life expectancy as a consequence of hip fracture, the proportion of the years of life lost is significantly higher in men than in women (70 vs. 59%) [5].

Patients with a fracture are at markedly elevated risk of a second fracture [8,9]; nonetheless, the interval between fractures generally seems sufficient for interventions aimed at reducing the risk of subsequent fractures to be effective [10,11].

The diagnosis of the disease relies on the quantitative assessment of bone mineral mass/density, which represents so far one major determinant of bone strength and thereby of fracture risk. However, only approximately half of fragility fractures occur in women meeting current criteria for osteoporosis based on BMD [12,13]. Part of this discrepancy may be explained by the fact that many osteoporotic fractures are precipitated by falls [14]; for instance, some 98% of hip fractures are the result of falls. Thus, the risk of osteoporotic fracture seems to be determined by the balance between bone strength and propensity for falling (Fig. 1).

2. Falls

Falls and fall-related injuries are common in elderly people [15]. It is estimated that 30 to 40% of generally healthy, community-living persons aged > 65 years experience a fall in any given year, and the rates are higher for those resident in nursing homes and persons aged > 75 years [16]. The incidence of falls among women increases sharply with age. One of the most powerful risk factor is muscle weakness, followed by a history of falls and gait deficit. Some medications may increase fall risk, including psychotropic drugs such as benzodiazepines, and cardiovascular drugs such as anti-arrhythmics, digoxin, and diuretics [17,18]. Environmental factors such as poor lighting, loose or frayed carpets, and trailing electrical cables may also increase the risk of falling [16] (Table 1).

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A meta-analysis evaluating the most effective training programme in reducing falls in the elderly showed that patients who undertook exercise programmes had lower fall rates than those who did not. The largest reductions were found in programmes with a high dose of exercise and in those which involved balance training. Exercise programmes that did not include walking reduced fall rates more than those that involved walking. The negative influence of walking on fall rate may be due to time spent walking taking the place of balance training. However, walking programmes have demonstrated other health benefits, including preventing bone loss in postmenopausal women [23]. Exercise training can also be effective in the very elderly. Indeed, a home exercise training programme reduced the number of falls by 35%, and in terms of injury prevention, participants aged ≥ 80 years benefited significantly more than those aged 65 to 79 years [24].

Whole body vibration may provide a means of reducing fall risk that is more acceptable to some elderly people than conventional exercise. However, to date no randomised controlled trial has assessed its effect on the numbers of falls.

Early studies suggested that wearing hip protectors reduced the incidence of hip fracture in elderly people living in institutional care. However, recent systematic reviews have indicated that hip protectors are not effective in community-dwelling individuals, and have cast doubt on their effectiveness in those living in institutions [25,26].

### 3. Nutrition

Nutritional deficiencies play a significant role in osteoporosis and fracture pathogenesis [27]. Undernutrition is often observed in elderly, and it appears to be more severe in patients with hip fracture than in the general aging population. A low protein intake could be particularly detrimental for the conservation of bone integrity with aging [28]. Protein undernutrition can favor the occurrence of hip fracture by increasing the propensity to fall as a result of muscle weakness and of impairment in movement coordination, by affecting protective mechanisms, such as reaction time, muscle strength, and thus reducing the energy required to fracture an osteoporotic proximal femur, and/or by decreasing bone mass [29]. Furthermore, a reduction in the protective layer of soft tissue padding decreases the force required to fracture an osteoporotic hip.

In a prospective study carried out on more than 40,000 women in Iowa, higher protein intake was associated with a reduced risk of hip fracture. The association was particularly evident with protein from animal rather than vegetal origin [30]. Regarding the relation with bone mineral mass, there is a positive correlation with protein intake has a favorable effect on BMD in elderly receiving calcium and vitamin D supplements [33]. Taken altogether, these results indicate that a sufficient protein intake is mandatory for bone health, particularly in elderly.

Undernutrition is linked also to the concept of frailty, which has received increasing attention in recent years [34]. Frailty involves a decreased reserve or resistance to stressors, resulting in increased vulnerability to adverse outcomes including falls, disability, dependency, and mortality [35]. Frailty involves also chronic undernutrition, sarcopenia, and reduced total energy expenditure. Low scores (< 27 points) on the Mini-Nutritional Assessment are associated with a two-fold increase in the risk of osteoporosis [36].

An operational definition of frailty has been proposed by Fried et al., and is based on five characteristics: unintentional weight loss, muscle weakness, reduced energy and endurance, slowness of gait, and low physical activity level [37] (Table 2). People with none
of these characteristics are considered to be robust, those with one or two as intermediate or prefrail, and those with three or more are frail. Both frailty and prefrailty are more prevalent in women than in men [37]. In the prospective Study of Osteoporotic Fractures, frail women were at increased risk of falls, all non-spine fractures, hip fractures, and death compared with robust women, after adjustment for potential confounders including age and BMD [38]. The associations between frailty and these adverse outcomes persisted among women > 80 years of age. An index based on data from the Study of Osteoporotic Fractures involves three components: weight loss (regardless of intent), reduced energy level, and inability to rise from a chair five times without using the arms [39]. This simpler index is able to predict falls, fractures, disability and death, and may enable the identification of high-risk women in clinical practice. A simple question like “Do you have impaired balance?” identified individuals at substantially increased risk of fracture, with approximately 40% of hip fractures attributable to self-reported impaired balance [40].

Intervention studies using supplementary feeding by nasogastric tube or parenteral nutrition, or even a simple oral dietary preparation that normalizes protein intake, can improve the clinical outcome after hip fracture. An oral protein supplement, which brought the intake from low to a level still below RDA (i.e. 0.8 g/kg body weight), avoiding thus the risk of an excess of dietary protein improved the clinical course in the rehabilitation hospitals, significantly lowering the rate of complications, such as bedsores, severe anemia, intercurrent lung or renal infections [41,42]. Thus, the total length of stay in the orthopedic ward and rehabilitation hospitals was significantly shorter by 25% in supplemented patients than in controls [41–43]. Normalization of protein intake, independently to that of energy, calcium and vitamin D, was in fact responsible for this more favorable outcome [42]. Finally, this normalization of protein intake was found to increase IGF-I, and even IgM concentrations [43] (Table 3, Fig. 2). Thus, the lower incidence of medical complications with the correction of protein intake insufficiency is also compatible with the hypothesis of IGF-I improving the immune status, as this growth factor can stimulate the proliferation of immunocompetent cells and modulate immunoglobulins secretion [44].

### 4. Vitamin D and calcium

In addition to a prominent role in calcium and phosphorus homeostasis [45], increasing attention has been focussed on the importance of vitamin D in skeletal muscle function [46–48]. Risk factors for vitamin D inadequacy include dietary deficiency and low exposure to sunlight, which may be due to lifestyle factors, living at high latitudes, cultural and religious practices of covering the skin surface, and skin pigmentation [49]. Elderly people have reduced capacity for cutaneous synthesis of vitamin D during skin exposure to UV radiation [50].

Low serum 25(OH)D levels, which is a reflection of poor vitamin D status predict increased risk of hip fracture. The risk increases with decreasing quartiles of serum 25(OH)D [51]. Vitamin D inadequacy is highly prevalent in many countries, especially among women with osteoporosis [45,52]. In postmenopausal Belgian women with osteoporosis (mean age 76.9 years), 91% had serum 25(OH)D levels below 80 nmol/L, and serum 25(OH)D concentration decreased significantly with age [53]. A low vitamin level is particularly found in elderly with a recent hip fracture [54]. Vitamin D supplementation, usually in combination with calcium, offers straightforward and inexpensive means of improving both sides of the bone strength/fall propensity balance [27,55]. However, the large number of studies and meta-analyses evaluating the clinical effectiveness of vitamin D and calcium supplementation in preventing fractures have produced discrepant results. Meta-analyses have also produced differing conclusions depending on the subsets of studies they included.

A meta-analysis included double-blind studies of supplementation with vitamin D with or without calcium, but studies that used active vitamin D metabolites were excluded [56]. High dose supplemental vitamin D reduced fall risk by 19% (pooled relative risk (RR) 0.81, 95% CI 0.71 to 0.92; n = 1921 from seven trials), whereas achieved serum 25(OH)D concentrations of 60 nmol/L or more resulted in a 23% fall reduction (pooled RR 0.77, 95% CI 0.65 to 0.90) (Fig. 3).

Another meta-analysis of 17 trials of calcium and calcium in combination with vitamin D (52,625 participants, 46,108 receiving the combination) indicated a 12% reduction in fractures of all types (RR 0.88, 95% CI 0.83 to 0.95) [57]. Trials reporting compliance rates of ≥ 80% showed a greater treatment effect of 24%. Treatment effect was also greater in people aged > 70 years compared with

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Table 2: Operational definition of frailty. The presence of three or more elements identifies frailty [37].

<table>
<thead>
<tr>
<th>Element</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss, sarcopenia</td>
<td>Unintentional loss of &gt; 5 kg in previous year</td>
</tr>
<tr>
<td>Exhaustion, poor endurance</td>
<td>Grip strength in lowest quintile (adjusted for gender and body mass index)</td>
</tr>
<tr>
<td>Slowness of gait</td>
<td>Self-report</td>
</tr>
<tr>
<td>Low level of physical activity</td>
<td>Time to walk 4 m in lowest quintile (adjusted for gender and height)</td>
</tr>
<tr>
<td></td>
<td>Kilocalories expended in physical activity per week in lowest quintile (calculated using standardised algorithm and adjusted for gender)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes (% baseline value)</th>
<th>Placebo</th>
<th>Protein supplements*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prealbumine</td>
<td>+56 ± 9</td>
<td>+86 ± 14</td>
<td>0.07</td>
</tr>
<tr>
<td>IGF-I</td>
<td>+34 ± 7</td>
<td>+86 ± 15</td>
<td>0.01</td>
</tr>
<tr>
<td>IgM</td>
<td>+40 ± 6</td>
<td>+66 ± 9</td>
<td>0.02</td>
</tr>
<tr>
<td>Proximal femur BMD</td>
<td>−4.7 ± 0.8</td>
<td>−2.3 ± 0.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Stay in rehabilitation hospital</td>
<td>54</td>
<td>33</td>
<td>0.02</td>
</tr>
<tr>
<td>Median of length of stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Protein supplements provided 20 g/day. All patients received 200,000 IU at baseline. Adapted from [43].

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**Fig. 2.** Correction of protein undernutrition, fracture risk and rehabilitation after fracture.
those aged 50 to 70 years, and in those living in care institutions (RR 0.76) compared with those living in the community (RR 0.94).

The benefit of treatment was also significantly greater with calcium doses \( \geq 1200 \text{ mg per day} \), or vitamin D doses \( \geq 800 \text{ IU per day} \).

In a Cochrane collaboration meta-analysis of eight trials involving 46,658 participants, the combination of vitamin D with calcium significantly reduced hip fractures (RR 0.84, 95% CI 0.73 to 0.96), and a subgroup analysis suggested that the effect was significant among those living in institutional care\[58\]. Meta-analysis of nine trials involving 24,749 participants suggested that vitamin D alone was unlikely to be effective in preventing hip fracture.

Overall, these analyses indicate that vitamin D and calcium supplementation can be effective in preventing falls and fractures in elderly people. Indeed, an adequate supply of vitamin D and calcium is essential for the maintenance of bone strength and skeletal muscle function. The likelihood of effectiveness of vitamin D and calcium supplementation increases with the degree of vitamin D inadequacy. The effectiveness of vitamin D and calcium supplementation also appears to increase with age. However, it should be borne in mind that renal insufficiency is common in the very elderly and may reduce conversion of vitamin D to its active form.

Poor adherence appears to be a major factor limiting the efficacy of vitamin D and calcium supplementation in clinical trials, and an even greater problem in clinical practice. Adherence to calcium supplementation may be lower than for vitamin D, partly because of gastrointestinal symptoms\[59\].

5. Anti-osteoporotic drugs

The efficacy of several agents to increase bone strength and reduce osteoporotic fracture risk has been established in a number of well-designed randomised clinical trials, largely carried out to meet regulatory requirements\[60\]. However, most such trials have included only a small proportion of very elderly patients. Evidence of efficacy has been generally most compelling for vertebral fractures. Evidence for nonvertebral fractures and particularly hip fracture, the most important and serious osteoporotic fracture in the very elderly, is more scant and less consistent\[61\].

Specific anti-osteoporotic drugs are widely underused in people at risk of osteoporotic fracture. For instance, in a recent study of 23,146 patients in Belgium hospitalised for hip fracture, only 6% of those not previously treated received a specific anti-osteoporotic drug after the fracture\[62,63\]. Data from the US National Health and Nutrition Examination Survey (NHANES), showed that only 12% of women aged \( \geq 85 \) years, and 17% of women aged \( \geq 65 \) years who had a history of fracture, were receiving treatment targeted to prevent bone loss\[64\]. Anti-osteoporosis treatment is not always targeted at those at greatest risk of fracture. Thus, in women aged \( \geq 60 \) years with hip, vertebral or wrist fracture, increasing age was associated with a reduced likelihood of receiving specific anti-osteoporosis treatment\[65\].

6. Critical pathway for fracture management in the elderly

A prevalent fracture is a major risk of fracture. But an osteoporotic fracture often remains undiagnosed and untreated. A clinical pathway in the frame of a fracture liaison service together with the orthopaedic team has been shown to be highly efficacious for diagnosis and treatment of osteoporosis in fragility fracture patients\[66\] (Fig. 4). A recent low-trauma fracture is used as a selection criterion to identify those patients at high risk of osteoporosis and of subsequent fracture, in order to propose tailored additional investigations and a preventive strategy in the orthopedic ward. In addition, through an interactive educational program for the patients and their families, awareness of the disease and compliance can be improved.

7. Efficacy of anti-osteoporotic drugs in the elderly

Evidence of efficacy of anti-osteoporotic drugs in the very elderly has come primarily from subgroup analyses, in some cases involving the pooling of data from more than one trial\[67\]. A review of published evidence has been published recently\[68\], as has a less formal analysis\[69\] (Table 4).
7.1. Bone resorption inhibitors

7.1.1. Alendronate

In a post-hoc analysis of the Fracture Intervention Trial, alendronate was associated with a 38% reduction in risk of vertebral fracture at 3 years in women aged ≥ 75 years [70]. Eight patients should be treated for 5 years with alendronate to prevent one new vertebral fracture (NNT = 8). No data are available in patients > 80 years. Analysing age-specific fracture rates in the alendronate and placebo groups using a Cox proportional hazards regression model suggested that the effect of alendronate on symptomatic vertebral and hip fractures was approximately constant across the age range of women in the study [71].

7.1.2. Risedronate

In the Hip Intervention Program, risedronate had no effect on the incidence of hip fracture in the subgroup of women aged ≥ 80 years recruited on clinical factors only, but without the densitometric diagnosis of osteoporosis [72]. In a pooled analysis of data for women aged ≥ 80 years from three trials, risedronate reduced the incidence of vertebral fracture by 81% at 1 year and 44% at 3 years, but had no effect on nonvertebral fractures [73]. Hip fractures were not reported separately in this analysis.

7.1.3. Ibandronate

No data are available on the antifracture efficacy of ibandronate in the very elderly.

7.1.4. Clodronate

In randomly selected community-dwelling women aged ≥ 75 years who did not need to have osteoporosis or any other known risk factors for fracture, clodronate had no effect on the incidence of hip fracture, but did reduce the risk of any clinical fracture by 20% (hazard ratio 0.80, 95% CI 0.68 to 0.94) and non-hip fractures by 29% (hazard ratio 0.71, 95% CI 0.57 to 0.87) at 3 years [74]. No data are available in patients ≥ 80 years.

7.1.5. Zoledronic acid

Once-yearly zoledronic acid reduced the risk of vertebral and hip fracture by 70 and 41%, respectively, versus placebo [75]. Adjusted odds ratio for vertebral fracture was 0.37 [95% CI, 0.22–0.52] in ≥ 75 years age group (for review [76]). In patients (mean age 74.5 years) with recent hip fracture, both vertebral and nonvertebral fracture risk was reduced by once yearly zoledronic acid infusion, although the reduction in hip fractures was not significant [77]. Interestingly, the rate of death was reduced by 28% in the zoledronic acid group, emphasising the impact of osteoporotic fractures on mortality.

7.1.6. Denosumab

The Receptor Activator of Nuclear kappa B ligand (RANKL) is an essential mediator of osteoclast differentiation, activation and survival. Denosumab is a RANKL-targeted, high-specificity, fully human monoclonal antibody. Given twice yearly subcutaneously, it significantly reduced risk of new vertebral, hip, and nonvertebral fractures over 3 years [78]. In osteoporotic women ≥ 75 years, denosumab reduced hip fracture risk by 62% [95% CI, 22–82%] [79].

7.2. Bone formation stimulator

7.2.1. Teriparatide

In a subgroup analysis of data from women aged ≥ 75 years, teriparatide treatment was associated with a significant 65% reduction in risk of new vertebral fracture, but had no effect on nonvertebral fractures after a median treatment duration of 19 months [73]. No data are available for teriparatide in patients ≥ 80 years.

7.3. Mixed action

7.3.1. Strontium ranelate

A preplanned pooled analysis of data from women aged ≥ 80 years showed significant reductions in relative risk of vertebral and nonvertebral fractures at 3 years of 32 and 31%,...
respectively [80]. As soon as at 1 year of treatment there were significant reductions in vertebral and nonvertebral fractures of 59 and 41%, respectively. The antifracture efficacy persisted over a 5 year period. There was an increased QALYs in this above 80 years age class [81].

7.4. Poor adherence to treatment
Older age may be associated with a greater risk of nonadherence [82,83]. A further issue for very elderly individuals is the need to meet the specific requirements for oral intake of bisphosphonates (fasting before and after intake, not sucking or chewing tablets, taking with a full glass of water, remaining upright for 30–60 minutes after intake) to prevent adverse effects on the mouth and oesophagus. These requirements may be particularly challenging for the very elderly. Intermittent dosing regimens for bisphosphonates may have the potential to reduce the inconvenience associated with daily oral dosing and could improve adherence to therapy [84–86], but adherence rates may still remain severely suboptimal. Hence, weekly oral alendronate and risedronate, and ibandronate given orally at monthly intervals or intravenously every 2 or 3 months, as well as once-yearly zoledronic acid may predict a better adherence and compliance [87,88]. Strontium ranelate, which has efficacy against hip and other nonvertebral fractures as well as vertebral fractures in the very elderly, is given by a simple daily oral dosing regimen without the special precautions associated with bisphosphonates.

8. Conclusions
The risk of osteoporotic fractures in the very elderly is determined by a large number of factors ranging from hazards in the home environment to frailty, poor balance, and bone fragility. The present situation in which many elderly people at high risk of fracture receive no treatment or highly inadequate treatment is not acceptable. Effective treatments are available, including exercise training, vitamin D, calcium and protein supplementation, and use of evidence-based anti-osteoporotic drugs. Optimising the use of such treatments could help to reduce the large and increasing burden of osteoporotic fractures in the very elderly.

Conflicts of interest
None.

References


