Prevention of hip fractures in osteoporosis

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Hip fracture is the major clinical consequence of osteoporosis. It is linked with decreased life expectancy and quality of life, placing an ever-increasing burden on health services. Few medications have unequivocally demonstrated their ability to reduce hip fracture risk in osteoporotic subjects. Daily alendronate and risedronate reduce hip fracture in patients with low bone mineral density (BMD) and prevalent vertebral fractures. Intravenous bisphosphonates have been developed in response to long-term poor adherence to oral anti-osteoporotic treatments. Once-yearly zoledronic acid reduces fracture rates at the spine, non-spine and hip locations. Strontium ranelate, the first drug to uncouple bone formation from bone resorption has also demonstrated its ability to reduce hip fractures in patients above 74 years old, with prevalent low BMD. Calcium and vitamin D supplementation are prerequisite for the management of elderly subjects and should always been associated to anti-resorptive or bone forming agents. Non-pharmacological management of osteoporosis is recommended, but it cannot be considered a substitute for pharmacological treatment of osteoporosis, not even in old age.

Key words: Osteoporosis - Hip fractures, prevention and control - Hip fractures, therapy - Disphosphonates - Strontium ranelate.

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Osteoporosis is widely recognized as a major public health concern. It is defined as a systematic skeletal disease characterized by bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] Although the diagnosis of the disease relies on the quantitative assessment of bone mineral density (BMD), which is a major determinant of bone strength, the clinical significance of osteoporosis lies in the fractures that arise.

Common sites for osteoporotic fracture are spine, hip, distal forearm and proximal humerus. The remaining lifetime probability in women at the menopause of a fracture at any one of these sites exceeds that of breast cancer (approximately 12%), and the likelihood of a fracture at any of these sites is 40% or more in developed countries,[2] a figure close to the probability of coronary heart disease. In the year 2000, there were estimated to be 620 000 new fractures at the hip, 574 000 at the forearm, 250 000 at the proximal humerus, and 620 000 clinical spine fractures in men and women aged 50 years or more in Europe. These fractures accounted for 34.8% of such fractures worldwide.[3]

Collectively all osteoporotic fractures

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accounted for 2.7 million fractures in men and women in Europe at a direct cost of ?36 billion.[4]

Whereas, many studies reveal an increase of the age-adjusted hip fracture incidence, recent studies specifically examined secular changes in the incidence of hip fracture in women and men. They suggest that despite an increase in the population at risk and in the mean age of hip fractured women there was a significant decrease in age-adjusted incidence in women, but not in men. These results, if confirmed, may suggest a reversal of the previously observed secular trend.[5]

Burden of hip fractures

It is widely recognized that osteoporosis and the consequent fractures are associated with increased mortality, with the exception of forearm fractures.[6]

Mortality among hip fracture patients is high, both during admission (range 4%[7] to 7%[8]) and after discharge; range 6%[9] to 10%[10, 11] 1 month after admission; 13%[9] to 17%[11, 12] 3 months after admission). Twelve months after admission mortality rates in Europe and North America span a range from 18%[13] to 20-25%[9, 14, 15] with Danish rates reaching a high 26-30%.[10, 12, 16] Men have a higher mortality (range 31%[17] to 34%[11, 14, 18] at 1 year) than women (range 17%[17] to 25%[18]). Mortality is also augmented by increasing old age,[9, 15, 19] comorbidity,[9, 20-22] and nursing home residence.[9] Some studies report an increased mortality for trochanteric compared with femoral neck fractures,[23-25] but other studies disagree.[17, 20, 21, 26, 27] Whites are reported to have a lower mortality than blacks.[9, 27, 28]

Mortality after hip fracture is highest during the first months after the injury and then declines.[9, 11, 14, 22, 29, 30] There is, however, also a long-term effect of hip fracture. It is reflected in a mortality, which 1 year after admission ranges from 20%[16, 31] to 30-34%,[11, 14, 32] and which is higher among men (25%) than among women (19%).[11] The duration of this long-term effect varies from study to study. Excess mortality is statistically significant 5 to 10 years after hip fracture in Danish

patients,[11] up to 1 year after hip fracture among Norwegian men and women, and up to 9 years after fracture among 75-84 year-old Norwegian women.[17] Among women in the U.S., excess mortality 5 years postfracture amounts to 9 deaths per 100 women.[22] In Canada, however, the standard mortality rate approaches unity in the 2nd year after admission.[14]

Most guidelines recommend comparing diseases and interventions in terms of their influence on quality adjusted life years (QALY).[33-35] The QALY estimator is an attractive outcome measurement in the field of osteoporosis,[36] because it offers the advantage of capturing at the same time the benefits from reduction in mortality and reduction in morbidity.[33]

Estimating individual preferences and utility loss attributable to prior fractures is nevertheless a difficult task. It is one of the main challenges in economic modelling in the field of osteoporosis.[37] Measuring and individual's quality of life and translating it into a utility value is not simple; it particularly depends on the instrument of measure used and the individual's perception of his or her health condition.

Different instruments to value QALY have been used. The main classification systems for preference-based measures are the QALY of well being (QWB), the Health Utilities Index (HUI) and the EuroQol (EQ-5D),[33] which have already been analyzed in detail.[38] Few studies had as a direct objective the comparison of techniques with each other.[39] Nevertheless, the EQ-5D is the most frequently used in the field of osteoporosis and is preferred for the reference values, because it has the advantage of being available for more osteoporosis related-conditions than HUI.[40]

Ten studies[35, 41-50] provided utility values following a hip fracture. Table I shows the utility values for each study as well as the calculation methods and sample size.

Most utility evaluations were made using time trade off (TTO)-weighted EQ-5D. Gabriel et al.[43] study compared some instruments, the HUI-II valuation found for those who had hip fracture in the past few years

was 0.68, compared with a valuation of 0.7 with TTO. The HUI-II valuation of Cranney et al.[50] was very similar, 0.67 and 0.71, at baseline and 2 months after fracture, respectively.

Brazier et al.[42] guidelines, recommended by the International Osteoporosis Foundation, reviewed all studies conducted before 2000. The authors suggest a value of 0.797 for loss in QALY attributable to a hip fracture during the 1st year. This value was drawn from the preceding 2000 study[52] that provided a more accurate estimate because it assessed the QALY value before and after the fracture. These authors also stressed that the QALY level prior to the fracture was lower than that of the healthy population (0.6 compared to 0.72),[42] which was not considered by other studies, like that of Gabriel et al.,[43] and that could therefore explain a greater reduction in QALY shown by the latter.

Among the studies conducted more recently than the guidelines, Murray et al.[54] study proves important, because it calculates the QALY level before and after the fracture, which means it is possible to obtain a reliable estimate of the annual loss in QALY amounting to 0.83, for a sample of 86 patients at 12 months. Studies by Zethraeus et al.[49] and Tidermark et al.[53] assessed the QALY loss at various time. Unfortunately, these studies did not assess the QALY level before the fracture, which makes the calculation of QALY loss uncertain. Nevertheless, the results of these two studies are similar to those emphasised recently by Borgstrom et al.[41] for fairly close periods of time. Moreover, this last study assesses the perceived QALY level before the fracture, which allows a more accurate estimate of the loss in QALY attributable to the fracture. This measurement alternates between 0.77 (by simple interpolation) and 0.83 (by consecutive assumption that assumes that the estimated QALY loss in reached after 1 month).

The financial burden of hip fractures has been investigated in various countries and settings. Recently, an international study assessed direct units costs associated with non-vertebral osteoporotic fractures in 5 European countries. The average direct cost of a hip fracture was valuated at € 9 674 (2002),[55] very close to what was previously shown in earlier studies.[56, 57] In a societal perspective, most of the authors consider that direct costs account for 27-66% of the overall expenses related to the global management of hip fracture. Based on this assumption, the global cost of a hip fracture, in a societal perspective, would sum up to € 13 587 (2002). Very few studies have investigated the indirect costs linked to hip fracture. However, when combining the direct medical costs reported in a large sample of males and females, stratified for age and gender[56] and the additional costs reported in another trial from the same county,[57] a global burden between € 16 457 and € 20 998 (2006), depending upon the age and gender of the patients, can be established.

The burden of hip fracture is obviously depending upon the respective national health services and the related resources utilization. However, when estimating direct costs of hip fractures in Belgium, France, Italy, United Kingdom and Spain, figures were amazingly close (from € 8 346 to € 9 907 [2002]).[55] When adjusting for 2006, the direct costs linked to hospitalization following a hip fracture were estimated between € 9 277 and € 17 117.

Similar trials were conducted in United States and Sweden. They respectively provide estimations between € 16 512 and € 18 945 (2006) for the US[58] and between € 12 162 and € 39 500 (2006) for Scandinavia.[59] A lower value of € 11 935 (2006) was provided for the United States, but did not take into account the burden linked to institutionalization of patients, following hip fractures. Most of these costs are related to the 1st year following the hip fracture. However, since a significant subset of the patients with a hip fracture will lose their independence and will not be able, any longer, to be community-dwelling, recurrent costs have to be taken into consideration, for the following years. We previously reported that the rate of institutionalization (nursing-homes) varies depending upon the age and the gender of the patients. For Belgian females, these rates varied from 5% (age: 50-59 years) up to 30%

TABLE I.—*Utility values associated with hip fracture.*

Study	Utility value	Method	No. of patients
NOF review [35]	First year: 0.38 Subsequent years: 0.85 Nursing home: 0.4	Experts judgements	
Gabriel *et al.*[43]	0.68 (±0.18) 0.61 (±-0.08) 0.72 (± 0.16) 0.7 (±-0.41)	HUI-II QWB VRS TTO	37 women (fracture in the last 5 years)
Salkeld *et al.*[51]	"Bad" hip fracture: 0.05 "Good" hip fracture: 0.31	EQ-5D-TTO	194 older women
Brazier *et al.*[52]	At 6 months: 0.49 (±0.32) At 1 year: 0.48 (±0.38)	EQ-5D-TTO	39
Tosteson *et al.*[48]	Without fracture: 0.91 (CI: 0.88-0.94) 12-24 months: 0.48 (CI: 0.32-0.64) >24 months: 0.79 (CI: 0.66-0.92) Overall: 0.63 (CI: 0.52-0.74)	TTO: U-Titer [63]	199 women 67 women
Cranney *et al.*[50]	Baseline: 0.67 (±0.12) At 2 months: 0.71 (±0.09)	HUI-II	10
Brazier *et al.*[42]	0.797 (CI: 0.65-1.01)	Systematic review, data from Brazier *et al.*[52]	
Zethraeus *et al.*[49]	At 2 weeks: 0.42 (±0.32) At 6 months: 0.64 (±0.27) At 9 months: 0.60 (±0.31) At 12 months: 0.58 (±0.31)	EQ-5D-TTO	86 65 58 46
Tidermark *et al.*[53]	At 1 week: 0.44 At 4 months: 0.55 At 17 months: 0.51	EQ-5D-TTO	90
Murray *et al.*[54]	Reference: 0.54 At 6 months: 0.45 At 12 months: 0.45 At 24 months: 0.5 Average annual loss of QALY: 0.83 (CI:0.72-0.96)	EQ-5D-TTO	117 103 86 55
Borgstrom *et al.*[41]	Perceived QALY before fracture: 0.8 (CI: 0.77-0.82) After fracture: 0.18 (CI: 0.15-0.2) At 4 months: 0.62 (CI: 0.59-0.66) At 12 months; 0.67 (CI: 0.64-0.7) Average annual loss of QALY: simple interpolation: 0.77 (CI: 0.74-0.79) Conservative hypothesis: 0.83 (CI: 0.8-0.86)	EQ-5D-TTO	277

NOF: National Osteoporosis Foundation; HUI: Health Utility Index; QWB; quality of well-being; VRS: vertical rating scale, TTO: time trade-off; U-titer: a utility assessment tool; "Bad" hip fracture: results in admission to a nursing home; "Good" hip fracture: maintaining independent living in the community; CI: confidence interval (95%).

(above 90 years).[56] Previous studies, conducted in other countries (Scandinavia), concluded to a lower degree of transfer to nursing-homes.

When taking these values into consideration, the cost of a hip fracture, for the years following the 1st year after the event, varies between € 1 525 (2006) for women between

50 and 59 years up to € 9 148, for women above the age of 90 years.

Pharmacological prevention of hip fractures

Calcium and vitamin D

The majority of studies that have investigated the effects of combined calcium and vitamin D supplementation in postmenopausal women have shown a reduction in fracture risk, providing that sufficient patient compliance (75-80%) was reached.[60-64]

The efficacy of combined calcium and vitamin D supplementation in reducing non-vertebral fracture rates has been demonstrated in three large, randomized, placebo-controlled, multicenter studies. Two of these studies involved institutionalized elderly patients, the Decalyos I[62, 65] and Decalyos II[61] studies, and one involved community-living elderly patients.[62]

Decalyos I enrolled 3 270 women, aged 69-106 years (mean: 84 years), all of whom were able to at least walk indoors with a cane.[62] All had inadequate dietary calcium intake (<800 mg/day; mean: 513 mg/day) at study entry, while 44% had vitamin D insufficiency—serum 25-hydroxyvitamin D [serum 25(OH)D] level <12 ng/mL, by radioimmunoassay (RIA). Randomization was 1:1 to 1 200 mg of calcium plus 800 IU of vitamin D daily (n=1 634) or to double placebo (n=1 636).

In the women completing 18 months' therapy (n=1 765), supplementation reduced hip fracture incidence by 43% (risk ratio [RR]: 0.57; 95% confidence interval [CI]: not indicated; P=0.043) and non-vertebral fracture incidence by 32% (RR: 0.68; 95% CI: not indicated; P=0.015).[62] Similar benefits were seen in the intention-to-treat analysis. The reduction in hip fracture risk was apparent after 10 months' therapy, while an effect on all non-vertebral fractures was seen within 2 months. Furthermore, it was noted that the incidence of hip fracture increased markedly with time in the placebo group, but remained stable in the calcium and vitamin D group.

Further analysis of Decalyos I at 36 months' follow-up confirmed the continued preventive effect of calcium and vitamin D on fracture risk. For patients remaining on treatment, risk of hip and non-vertebral fractures continued to be significantly reduced (RR: 0.61 and 0.66, respectively; 95% CI: not indicated; both P<0.01). In the intent-to-treat analysis, similar risk reductions were observed (RR: 0.77 and 0.83, respectively; 95% CI: not indicated; both P<0.02).[65]

Decalyos II had a similar design to Decalyos I, with the exception that randomization was 2:1 to calcium and vitamin D vs placebo and that the study duration was 2 years.[61] Of the 639 enrolled patients (610 randomized), 66% had an inadequate intake of both calcium (<800 mg/day) and vitamin D (serum 25(OH)D level [by RIA] <12 ng/mL). Hip fractures occurred in 27 out of 393 (6.9%) women in the calcium and vitamin D group, compared with 21 out of 190 (11.1%) in the placebo group. The difference in the cumulative probability of hip fracture did not achieve statistical significance (RR: 0.69; 95% CI: not indicated; P=0.07). Hip fracture risk was reduced in the calcium and vitamin D group from about 9 months, a finding consistent with that in Decalyos I. The magnitude of reduction in hip fracture risk was also similar to that seen in Decalyos I. The incidence of non-vertebral fractures was comparable in the two treatment groups. Femoral neck BMD remained unchanged in the calcium and vitamin D group (mean change: +0.29%/year), but decreased in the placebo group (-2.36%/year). The mean difference between the two treatment groups was not statistically significant (95% CI: 0.44; 5.75%).

In contrast to the Decalyos studies, the study by Dawson-Hughes et al.[63] involved healthy, elderly, ambulatory men and women aged >65 years (n=389; mean age: 71 years) living in the community. Levels of insufficiency were not as profound as those documented in the Decalyos studies. Randomization was 1:1 to calcium 500 mg plus vitamin D 700 IU or placebo, with follow-up and treatment planned for 3 years. Non-vertebral fractures were sustained by 11 (5.6%) patients in the calcium and vitamin D group, com-

pared with 26 (13.3%) in the placebo group (RR of first fracture: 0.5; 95% CI: 0.2-0.9; P=0.02). As in the Decalyos studies, supplementation also led to significant improvements in biochemical parameters and BMD.

Results of trials assessing fracture reduction with vitamin D alone have been equivocal.[66-68] In a recent randomized, double-blind, placebo-controlled study, vitamin D 100 000 IU every 4 months reduced the risk of first hip, wrist or forearm, or vertebral fractures by 33% (RR: 0.67; 95% CI: 0.48-0.93; P=0.02).[67] Similarly, in a controlled trial in elderly Finnish subjects, annual intramuscular injections of high doses of vitamin D (150 000-300 000 IU) reduced fracture rates by approximately 25% (RR: 0.75; 95% CI: not indicated; P=0.03),[68] although the benefits were limited to fractures of the upper limbs and ribs and to women only. No reduction in the risk of hip fractures was seen in a randomized, double-blind placebo-controlled trial of vitamin D (400 IU/day) alone in an elderly community-dwelling population (n=2 578; mean age 80 years) in the Netherlands (RR: 1.18; 95% CI: 0.81-1.71; P=0.31).[66]

Current evidence suggests the role that calcium and vitamin D play in fracture prevention is not attributable to calcium alone[69, 70] and a meta-analysis of data from 9 randomized clinical trials, including a total of 53 260 patients, found that supplementation with vitamin D alone was not sufficient to significantly reduce the risk of hip fracture in postmenopausal women.[71] However, the same study found that combined supplementation with vitamin D and calcium reduced the risk of hip fracture by 28% and the risk of non-vertebral fracture by 23% compared to supplementation with vitamin D alone. The meta-analysis estimated the number needed to treat (NNT) to prevent one adverse outcome to be 276 for hip fractures and 72 for non-vertebral fractures.[71]

Two recent studies, the RECORD study and the Women's Health Initiative (WHI), both of which were included in the meta-analysis, have reported results which appear to show that combined vitamin D and calcium supplementation is not effective in fracture prevention.[60, 72] However, neither study

targeted individuals at high fracture risk and in both the adherence was poor. The RECORD trial did not assess vitamin D levels or PTH response, so it is unknown whether subjects had vitamin D insufficiency. In addition, the number of fractures within this trial was low and together with the poor adherence, suggests that the study was underpowered. The WHI, whilst not showing a reduction in the risk of fractures with supplementation (1 000 mg calcium, 400 IU vitamin D3 daily), did find significantly greater preservation of hip BMD in women in the treatment group compared to those taking a placebo. Importantly, the WHI trial was carried out in healthy postmenopausal women with an average calcium intake >1 000 mg per day, 80% of whom were <70 years old. In addition, vitamin D status at baseline was unknown in all but 1% of individuals, so it is not possible to judge the level of vitamin D insufficiency with certainty in this study population. The administered dosage of vitamin D in this study was 400 IU, a dose shown in other studies to be insufficient to have an effect on fracture rate.[66, 73, 74] Finally, treatment compliance (defined as use of 80% or more of the assigned study medication) was low, estimated as <60%. Importantly, when analysis was carried out on only those subjects who were compliant a significant (29%) reduction in hip fracture risk compared to the placebo group was found.

In order to reduce fracture risk, combined supplementation should be administered to those at increased risk of fracture at doses adjusted depending on baseline levels, but potentially in the region of 800 IU of vitamin D and 1 000-1 200 mg of calcium daily.[75]

The vast majority of evidence for efficacy of anti-osteoporotic treatments is based upon combining treatment with calcium and vitamin D supplementation.[76-82] Vitamin D deficiency in humans and animals has been shown to reduce the response to some treatments for osteoporosis. In addition, animal studies have shown that the efficacy of bisphosphonates was blunted when the animals were exposed to a vitamin D deprived diet.[83] It is concluded, therefore, that anti-osteoporotic treatments should be used in combi-

nation with calcium and vitamin D supplementation. Little evidence is available regarding the combination of antiosteoporotic treatments with calcium alone or vitamin D alone.

Bisphosphonates

The anti-fracture efficacy of alendronate has been best established in two large populations of postmenopausal women, one with and one without pre-existing vertebral fractures.[84, 85] The daily dose of alendronate was 5 mg for the first 2 years and 10 mg thereafter. In the study including 2 027 women with established osteoporosis, *i.e.* with prevalent vertebral fracture(s) at baseline, alendronate reduced the incidence of new vertebral fractures by 47% (RR: 0.53; 95% CI: 0.41-0.68). The incidence of vertebral fractures with clinical symptoms was similarly reduced (RR: 0.46; 95% CI: 0.28-0.75). There was no reduction in the overall risk of non-vertebral fractures (RR: 0.8; 95% CI: 0.63-1.01), but hip fracture incidence was also reduced (RR: 0.49; 95% CI: 0.23-0.99) as was wrist-fracture risk (RR: 0.52; 95% CI: 0.31-0.87).[84] Estimation of the effect on hip fracture was not precise and the CI correspondingly wide, reflecting that the number of fractures (33 in total) was small.

The anti-fracture efficacy of alendronate was also demonstrated in 4 432 women with low bone mass, but without vertebral fractures at baseline treated for 4 years (5 mg daily during the first 2 years, then 10 mg daily). The reduction in the incidence of radiological vertebral fractures was 44% (RR: 0.56; 95% CI: 0.39-0.8). However, the reduction in clinical fractures was not statistically significant in the whole group, but well among women with initial T-scores <-2.5 at the femoral neck (RR: 0.64; 95% CI: 0.5-0.82). No reduction was observed in the risk of non-vertebral fractures (RR: 0.88; 95% CI: 0.74-1.04).[85]

Risedronate efficacy has been extensively tested in double-blind placebo-controlled trials. Risedronate at the dose of 5 mg daily for 3 years has thus been shown to significantly reduce the vertebral fracture risk in established osteoporosis as compared with placebo. In women with at least one vertebral fracture at baseline, the relative reduction of new vertebral fractures was 41% (RR: 0.59; 95% CI: 0.42-0.82), and 39% for non-vertebral fractures (RR: 0.61; 95% CI: 0.39-0.94).[78] In women with at least two vertebral fractures at baseline, the risk of new vertebral fractures was reduced by 49% (RR: 0.51; 95% CI: 0.36-0.73) but, in this study, the effect on new non-vertebral fractures was not significant (RR: 0.67; 95% CI: 0.44-1.04).[86] Risedronate has also been shown to decrease the incidence of hip fractures in a controlled trial specifically designed for that purpose. Hip fracture reduction was only observed in women with documented osteoporosis, however. In this placebo-controlled study involving 5 445 women 70-79 years old who had osteoporosis and risk factors for falls, it was shown that risedronate at 2.5 mg/day or 5 mg/day for 3 years (the actual mean duration of treatment was 2 years) lowered the relative risk of hip fracture by 40% (RR: 0.6; 95% CI: 0.4-0.9). There was no dose effect and, interestingly, the effect was greater in the group of women who had a vertebral fracture at baseline (RR: 0.4; 95% CI: 0.2-0.8). In the same study, however, there was no significant effect of risedronate in 3 886 women >80 years old (RR: 0.8; 95% CI: 0.6-1.2), but these patients were essentially selected on the basis of the presence of at least one risk factor for hip fracture, such as difficulty standing from a sitting position, a poor tandem gait, etc. rather than on the basis of low BMD or prevalent fractures.[87]

So far, the only direct comparison of bisphosphonates in a randomized clinical trial is based on surrogate endpoints (*e.g.* changes in BMD and markers of bone turnover).[88] The association between changes in these surrogates and subsequent fracture reduction is not consistent across studies.[89, 90] Unlike randomized clinical trials based on surrogate endpoints, observational studies of large populations provide the opportunity to use major disease endpoints (*e.g.* hip fracture) as the outcome of interest.

Since the once-a-week dosing regimens of both risedronate and alendronate have been available in the US since 2002, an observational study across multiple US health plans

was conducted to observe the incidence of hip and non-vertebral fractures among women aged 65 and over following initiation of therapy with once-a-week dosing of either risedronate or alendronate.

The RisedronatE and ALendronate (REAL) cohort study was a retrospective observation of bisphosphonate patients within healthcare utilization records in the United States, including two cohorts: women (ages 65 and over) receiving risedronate (n=12 215) or alendronate (n=21 615). Cox proportional hazard modelling was used to compare the annual incidence of non-vertebral fractures and of hip fractures between cohorts, adjusting for potential differences in risk factors for fractures.

There were 507 non-vertebral fractures and 109 hip fractures. Through 1 year of therapy, the incidence of non-vertebral fractures in the risedronate cohort (2%) was 18% lower (95% CI: 2-32%) than in the alendronate cohort (2.3%). The incidence of hip fractures in the risedronate cohort (0.4%) was 43% lower (95% CI: 13-63%) than in the alendronate cohort (0.6%).

The authors concluded that patients receiving risedronate have lower rates of hip and non-vertebral fractures during their first year of therapy than patients receiving alendronate.[91]

However, the oral bisphosphonates are associated with stringent dosage and administration procedures, and some patients may experience upper gastrointestinal adverse effects following administration.[92, 93] Consequently, about half of patients discontinue daily bisphosphonate therapy within 1 year, which negatively affects treatment outcomes, leading to a reduced anti-fracture effect.[94] Improving patient adherence to osteoporosis therapy is a complex process that involves effective patient/provider communication, association of treatment with expected benefits and/or positive treatment feedback (*i.e.* using measurements of markers of bone turnover or BMD measurements).[95] Another primary component of improving adherence is to use simplified or user-friendly treatment programs. It has been found across a range of therapeutic areas

that adherence to medication is inversely related to frequency of dosing.[96, 97]

Zoledronic acid is one of the most potent bisphosphonates that is currently available for clinical use. It is currently approved as an intravenous treatment for hypercalcemia of malignancy and/or metastatic bone diseases. In Paget's disease of bone, a single infusion of zoledronic acid has been shown to produce more rapid, more complete and more sustained response, than daily treatment with risedronic acid.[98] In a Phase II study, performed in postmenopausal women with low BMD, increases in BMD were recorded for intravenous doses of zoledronic acid 0.25 mg, 0.5 mg or 1 mg at 3-month intervals, with values for the spine being 4.3-5.1% higher than those in the placebo group, and values for the femoral neck being 3.1-3.5% higher than those in the placebo group.[99] Biochemical markers of bone resorption were significantly suppressed throughout the study (12 months) in all of the zoledronic acid groups. The most important finding of this study was that a single baseline dose of zoledronic acid 4 mg produced equivalent suppression of bone turnover and increases in bone mass to the more frequently administered smaller doses of the same agent. These findings strongly suggest that this agent may be able to be given as infrequently as once a year for osteoporosis therapy.

This hypothesis was tested in a double-blind, placebo-controlled trial, where 3 889 patients (mean age: 73 years) were randomly assigned to receive a single 15-min infusion of zoledronic acid (5 mg) and 3 876 were assigned to receive placebo at baseline, at 12 months, and at 24 months; the patients were followed until 36 months. Primary end points were new vertebral fracture (in patients not taking concomitant osteoporosis medications) and hip fracture (in all patients). Secondary end points included BMD, bone turnover markers, and safety outcomes.

Treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% during a 3-year period, as compared with placebo (3.3% in the zoledronic-acid group *vs* 10.9% in the placebo group; relative risk: 0.3; 95% CI: 0.24 to 0.38) and reduced

the risk of hip fracture by 41% (1.4% in the zoledronic-acid group *vs* 2.5% in the placebo group; hazard ratio: 0.59; 95% CI: 0.42 to 0.83). Non-vertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively (P<0.001 for all comparisons). Zoledronic acid was also associated with a significant improvement in BMD and bone metabolism markers.[100]

Strontium ranelate

It has been suggested that strontium ranelate may inhibit bone resorption and stimulation of bone formation, suggesting that, for the first time, a chemical entity used in the treatment of osteoporosis could be targeted to an uncoupling of the bone remodeling process.[101]

Strontium ranelate has been investigated in a large Phase III program that includes two extensive clinical trials for the treatment of severe osteoporosis: Spinal Osteoporosis Therapeutic Intervention (SOTI) aimed to assess strontium ranelate's effect on the risk of spine fractures, and Treatment of Peripheral Osteoporosis (TROPOS) aims to evaluate the effect of strontium ranelate on non-spine fractures. Both studies were multinational, randomized, double-blind and placebo-controlled, with two parallel groups (strontium ranelate 2 g/day *vs* placebo), a study duration of 5 years, and the main statistical analysis planned after 3 years.

A total of 1 649 patients were included in SOTI, with a mean age of 69 years, and 5 091 patients were included in TROPOS, with a mean age of 77.[102]

The primary analysis of the SOTI study, evaluating the effect of strontium ranelate 2 g on spine fracture rates, revealed a 41% reduction in relative risk of experiencing a first new spine fracture, throughout the 3-year study, compared with placebo (139 patients with spine fracture *vs* 222, respectively [RR: 0.59; 95% CI: 0.48-0.73] in the intent-to-treat population). This anti-fracture efficacy of strontium ranelate was demonstrated from the 1st year, with a 49% reduction in RR of experiencing a first new fracture

with strontium ranelate, compared with placebo (RR: 0.51; 95% CI: 0.36-0.74).[81]

The primary analysis of the peripheral study, evaluating the effect of strontium ranelate 2 g/day on non-spine fracture, showed that, in the entire sample, RR was reduced by 16% for all non-spine fractures (RR: 0.84; 95% CI: 0.7-0.99), and by 19% for major non-spine fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus; RR: 0.81; 95% CI: 0.66-0.98) in strontium ranelate patients, compared with the placebo group. In a posthoc analysis requested by the European Committee for Medical Products for Human (CHMP), including 1 977 women at high risk of hip fracture (≥74 year of age and femoral neck BMD T score ≥-3, corresponding to -2.4 according to National Health and Nutrition Examination Survey reference), the relative risk reduction for hip fracture was 36% (RR: 0.64; 95% CI: 0.41-0.99). The relative risk of spine fractures was reduced by 39% (RR: 0.61; 95% CI: 0.51-0.73) in the 3 640 patients with spinal X-rays, and by 45% in the subgroup without prevalent spine fracture (RR: 0.55; 95% CI: 0.39-0.77).

Non-pharmacological intervention and risk factor modification

Non-pharmacological prevention of fractures must be considered as a long-term treatment of osteoporosis, not only for postmenopausal women but also from childhood through adolescence, premenopause and perimenopause.

In 1995, risk factors for hip fracture were evaluated in a large prospective observational study.[103] These women were followed at 4-month intervals for 4.1 years. Besides expected risk factors like maternal history of hip fracture, personal history of any fracture, or low bone density, many lifestyle habits were significantly associated with a risk of hip fracture. Women who regularly walked for exercise had a 30% lower risk of fracture (RR: 0.7; 95% CI: 0.5-0.9). Those who spent 4 h per day or less on their feet had an increased risk of fracture (RR: 1.7; 95% CI: 1.2-2.4). Risk of hip fracture was also increased in women

with: high caffeine intake (RR: 1.3; 95% CI: 1-1.5 per 190 mg/day); current use of long-acting benzodiazepines (RR: 1.6; 95% CI: 1.1-2.4) or inability to rise from a chair (RR: 2.1; 95% CI: 1.3-3.2). Some factors, that were initially associated with a risk of hip fracture in age-adjusted models like current smoking or alcohol ingestion, were no longer significant after adjustment for other variables.

The Epidemiology of Osteoporosis (EPIDOS) prospective study examined the risk factors for hip fracture in 7 575 women, aged 75 years or older, during an average of 1.9 years of follow-up.[104] In age-adjusted multivariate analysis, neuromuscular and visual impairments were significant and independent predictors of the risk of hip fracture: slower gait speed (RR: 1.4; 95% CI: 1.1-1.6); difficulty walking (RR: 1.2; 95% CI: 1-1.5, for 1 point on the difficulty score); reduced visual acuity (RR: 2; 95% CI: 1.1-3.7, for acuity £ 2/10); small calf circumference (RR: 1.5; 95% CI: 1-2.2). Anxiolytic-drug use was significantly associated with the risk of hip fracture (RR: 1.4; 95% CI: 1.1-2), but this life habit was no longer significant in the multivariate analysis.

More recently, the Os des Femmes de Lyon (OFELY) study identified independent predictors of all osteoporosis-related fractures in a cohort of 672 healthy postmenopausal women aged 59.1±9.8 years, prospectively followed for 5.3±1.1 years.[105] Seven independent predictors of incident osteoporotic fractures were identified: age >65 years (odds ratio [OR]: 1.9; 95% CI: 1.04-3.46); past falls (OR: 1.76; 95% CI: 1-3.09); total hip BMD £0.736 g/cm² (OR: 3.15; 95% CI: 1.75-5.66); left grip strength £0.6 bar (OR: 2.05; 95% CI: 1.15-3.64); maternal history of fracture (OR: 1.77; 95% CI: 1.01-3.09); low physical activity (OR: 2.08; 95% CI: 1.17-3.69) and personal history of fragility fracture (OR: 3.33; 95% CI: 1.75-5.66). Other lifestyle habits, i.e. smoking, alcohol, tea or coffee consumption, were not associated with an increased fracture risk.

Low protein intake and malnutrition in the elderly have been associated with significant bone loss, at both femoral and spine sites, and increased risk of femoral fractures.[106, 107] Recently, the role of dietary protein intake in osteoporotic hip fracture was evaluated in 1 167 patients 50-89 years of age (831 women) with hip fracture and 1 334 controls (885 women).[108] Diet was assessed using a specific questionnaire. The OR of hip fracture decreased across increasing quartiles of total protein intake for participants 50-69 years of age: (OR: 1; reference); (OR: 0.51; 95% CI: 0.3-0.87); (OR: 0.53; 95% CI: 0.31-0.89); (OR: 0.35; 95% CI: 0.21-0.59). No similar associations were observed in participants 70-89 years of age.

In a recent review of non-pharmacological prevention of osteoporotic fractures, Deprez et al. emphasize the importance of falls as risk factor for non-vertebral and mainly hip fractures.[109] They remind us that falls occur at least once a year in 30% of individuals older than 65 years and in 50% of those older than 80 years of age, with a 5-6% fracture incidence. They consider environmental risk factors (inappropriate clothing, obstacles at home, slippery shower, the use of psychotropic agents with long half-lives, etc.) or patient-related factors (lower limb weakness, neurological disturbances, etc.) and review many clinical tools that can be used to evaluate the risk of falls. Lower-limb dysfunction deserves specific attention, because it is associated with increased risk for hip fracture in men (OR: 3.4; 95% CI: 2.1-5.4)[110] and in women (OR: 1.7; 95% CI: 1.1-2.8)[111] and can be largely modified by a therapeutic intervention. In 1 016 women and men, aged 65 to 97, a program of muscle-strengthening and balance-retraining exercises performed at home in 3 weekly 30-min sessions reduced by 35% both the number of falls (incident rate ratio [IRR]: 0.65; 95% CI: 0.57-0.75) and the number of fall-related injuries (IRR: 0.65; 95% CI: 0.53-0.81).[112] This program was most effective in patients aged 80 and older.

The increased risk for hip fracture associated with hitting the hip in a fall (OR: 97.8; 95% CI: 31.7-302) and the reduced risk associated with high body mass index (OR: 0.6; 95% CI: 0.4-0.9, for each additional 4 kg/m²) suggest that preventive efforts for older patients at high risk might include protective hip pads to reduce the force on the hip in a fall.[113] In 1997, Lauritzen et al. described a

significant reduction of the hip fracture risk (RR: 0.44; 95% CI: 0.21-0.94) with the use of hip protectors in a randomized trial (444 women; 221 men).[114] Similar results were published in 2000 with a 60% reduction of the hip fracture risk in the hip-protector group (RR: 0.4; 95% CI: 0.2-0.8) in 1 801 ambulatory, frail elderly patients with a mean age of 82 years.[115] These results were not confirmed in other trials that found hip protectors having no effect for the prevention of the first[116] or of a second hip fracture.[117] Deprez *et al.* underline that differences between these studies may be due to differences in randomization methods: most of the studies showing a positive effect of hip protectors used the study centers as the randomization unit, whereas most of the studies that found no benefit used individual randomization.[109] If an entire center uses hip protectors, it increases the probability that the devices are properly positioned and worn with an optimal compliance, day and night.

Conclusions

From a societal perspective, several studies have concluded that osteoporosis places an ever-increasing burden on health services and that this disease with its related costs should be regarded as a major health issue. Patients with hip fractures often face a reduced life expectancy, severe physical impairment and decreased quality of life. Since the prevalence of osteoporosis and, consequently, the incidence of hip fractures might sharply increase in most developed and developing countries, there is an urgent need for setting up effective and efficient prophylactic strategies.

During the last decade, several new therapeutic options have emerged, suggesting their ability to reduce hip fractures while maintaining a positive risk/benefit balance.

Calcium and vitamin D supplementation should be a first-line strategy for the management of osteoporosis. The high prevalence of vitamin D deficiency in elderly European subjects, combined with the low marginal cost of a calcium-vitamin D sup-plementation suggest that, after the age of 65, calcium and vitamin D should be systematically offered to all postmenopausal women, either alone or, if needed, in combination with another therapeutic regimen. Oral alendronate and risedronate reduce hip fractures in women with established osteoporosis (low BMD and prevalent fractures). A recent pragmatic study suggested that weekly risedronate might induce lower rates of hip fractures during the 1st year of therapy than alendronate would do. Do to the poor long-term adherence to oral bisphosphonates therapy, intravenous administration of zoledronic acid, showing a clear reduction in vertebral, non-vertebral and hip fractures, might be a preferred option compared to oral daily or weekly formulations. Strontium ranelate reduces vertebral, non-vertebral and hip fractures in a wide scatter of patients, with an excellent safety profile. This compound, uncoupling for the first time bone formation (simulated) from bone resorption (decreased), will likely become the most serious competitor to intravenous bisphosphonates for the management of osteoporosis. Risk factor alterations, including fall prevention strategies, are recommended. However, no anti-fracture efficacy of such strategy has been clearly demonstrated. Subsequently, fall prevention cannot be considered a substitute for pharmacological treatment of osteoporosis, not even in old age.

Riassunto

Prevenzione delle fratture dell'anca nell'osteoporosi

La frattura dell'anca è la principale conseguenza clinica dell'osteoporosi. Essa è legata a una diminuita aspettativa di vita e a un peggioramento della qualità di vita, rappresentando un carico crescente per la sanità pubblica. Pochi farmaci si sono dimostrati inequivocabilmente in grado di ridurre il rischio di frattura dell'anca nei soggetti con osteoporosi. La somministrazione giornaliera di alendronato e il risedronato riduce il rischio di frattura dell'anca nei soggetti con bassa densità minerale ossea e fratture vertebrali prevalenti. La somministrazione endovenosa di bifosfonati è stata sviluppata in risposta alla scarsa aderenza a lungo termine ai trattamenti anti-osteoporosi per via orale. La somministrazione una volta all'anno di acido zoledronico riduce i tassi di frattura del-

la colonna vertebrale, dell'anca e di altre sedi ossee. Anche lo stronzio ranelato, il primo farmaco per disaccoppiare la formazione ossea dal riassorbimento osseo, si è dimostrato in grado di ridurre le fratture dell'anca nei pazienti con oltre 74 anni di età e con prevalente bassa densità minerale ossea. L'apporto di calcio e di vitamina D rappresenta un pre-requisito per la gestione dei soggetti più anziani e dovrebbe essere associato sempre a farmaci anti-riassorbimento osseo o favorenti la deposizione ossea. La gestione non farmacologia dell'osteoporosi viene raccomandata, ma non può essere considerata un'alternativa al trattamento farmacologico, soprattutto nelle età più avanzate.

Parole chiave: Osteoporosi - Anca, fratture, prevenzione e controllo - Anca, fratture, terapia - Bifosfonati - Strontium ranelato.

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