

CONSENSUS PAPER

Background for studies on the treatment of male osteoporosis: state of the art

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Abstract

Male osteoporosis represents an important, although long underestimated, public health problem. Both in men and in women aging is accompanied by continuous bone loss and by an exponential increase in the incidence of osteoporotic fracture, with a female to male incidence ratio of about 2 to 3 to 1 in the elderly for hip and vertebral fractures. Morbidity after osteoporotic fractures appears to be more serious and mortality more common in men than in women. To date, no single treatment has been proved to be effective and safe in published prospective studies.

The present report, based on a systematic search of the literature on male osteoporosis, summarises the state of the art on the clinical consequences of male osteoporosis and its risk factors, in relation to the present state of knowledge about female osteoporosis. This constitutes the background for the design of rational clinical development strategies for therapeutic interventions in male osteoporosis. From this review of the literature it is apparent that notwithstanding the existing sex differences in pathophysiology of osteoporosis and the difference in age-specific incidence of osteoporotic fractures, there are also important similarities between osteoporosis in women and men. The higher incidence of fracture in women than in men results from quantitative differences in risk factors rather than from different risk factors. Even though there are sex differences in bone geometry, incidence of fracture seems to be similar in men and women for a same absolute areal bone mineral density. However, the lack of data on the changes in fracture rates in men resulting from pharmacological intervention, leading to changes in bone mineral density or bone turnover, remains the main limitation for extrapolation of established treatment outcomes from women to men.

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Osteoporosis has long been considered a disease of women. More recently, there has been increasing recognition that osteoporotic fractures in men also represent an important public health problem.¹⁻⁴

To date, published prospective studies have not adequately proved any single treatment to be effective and safe. Nevertheless, recently, useful information has been obtained on the epidemiology of male osteoporotic fractures and their relation to risk factors such as bone mineral density. Several large scale prospective observational studies including both men and women are presently being conducted, such as the Rotterdam study,⁵ the Malmö study,⁶ and the Dubbo study.⁷

The present document is based on a systematic search of the literature on male osteoporosis complemented, when appropriate, by relevant recent data published in abstract form. It aims at summarising the state of the art on the clinical consequences of male osteoporosis and its risk factors, in relation to the present state of knowledge about female osteoporosis. This constitutes the background for the design of rational clinical development strategies for therapeutic interventions in male osteoporosis. Such strategies should take sufficiently into account the particularities of male osteoporosis while taking advantage, whenever possible, of the considerable recent progress achieved in the treatment of female osteoporosis.

The burden of illness

INCIDENCE OF HIP FRACTURES IN MEN

An age related increase in the incidence of hip fracture is found in both men and women, with a female to male incidence ratio of about 2 to 3 to 1 in the elderly. In fact, the hip fracture incidence in men reaches the same level as in women, at an age about 5 to 6 years older with, for instance, 80 year old men having the same hip fracture risk as 75 year old women.⁸⁻⁹ Numerous reports on the incidence of hip fracture in North America and different European countries have come to similar conclusions.¹⁰⁻¹⁸

The lifetime risk of hip fracture in men has been estimated as 6% compared with 17.5% in women.¹⁹ A recent lifetime risk estimate that takes into account the projected life expectancy of the male and female population, came to a

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slightly higher estimation of the lifetime risk of hip fracture: 22.7% in women *v* 11.1% in men at age 50; 20.0% in women *v* 10.1% in men at age 80. The difference in lifetime risk between men and women is explained by both a lower age-specific incidence and the shorter life expectancy in men.²⁰

Two projections of the expected number of hip fractures world wide have been made. Cooper *et al* estimated the expected number of fractures to be 3.94 million in 2025,^{21a} of which 1.16 million are expected in men and 2.78 million in women. Gullberg *et al* estimated the number of fractures as 1.26 million (338 000 men and 917 000 women) in 1990.²² If cyclical trends with increased age-specific incidence of hip fractures, which have been reported to be more pronounced in men than in women, are taken into account, the number of hip fractures might range between 7.3 and 21.3 millions by 2050; the percentage increase will be greater in men than in women.²²

INCIDENCE OF VERTEBRAL FRACTURES IN MEN

For vertebral fractures a clear distinction should be made between clinically diagnosed fractures and vertebral deformities. Information on clinical vertebral fractures in both sexes is limited. Cooper *et al* reported the age adjusted rate in women (145/100 000 person-years) to be almost twice that in men (73/100.000 person-years)^{21b}; similar observations have been made by Bengnér *et al*.²³ As with the observation on hip fractures, there seems to be a 5 to 10 year age shift in the age-specific incidence of clinical vertebral fractures.

O'Neill *et al* have reported the prevalence of vertebral deformity in European men and women.²⁴ Based on the McCloskey method, the mean centre prevalence of all deformities was 12% in women (range 6–21%) and 12% in men (range 8–20%). The prevalence increased with age in both sexes, though the gradient was steeper in women. There was, however, substantial geographical variation, with the highest rates in Scandinavian countries. The risk of vertebral deformity was greater in younger men than in women, possibly as a result of greater exposure to trauma during their working life, implying that these deformities probably should be considered as “traumatic”. A similar overall prevalence of vertebral deformities in both sexes, with less progression to severe vertebral deformities in men, was reported by Burger *et al*.²⁵ Confirming the finding of the prevalence studies, figures on the prospectively assessed true incidence of vertebral deformities have recently been reported²⁶: 1.00 (95% confidence interval (CI) 0.84 to 1.19) woman and 0.56 (0.46 to 0.73) men had an incident deformity per 100 years' follow up.

INCIDENCE OF OTHER FRACTURE TYPES IN MEN

A much larger difference in sex-specific incidence has been reported for the incidence of wrist fracture,⁶ with up to a fourfold difference.

The overall incidence of symptomatic fractures (all types confounded) in elderly men and women was evaluated in the Dubbo osteoporosis

epidemiology study.²⁷ An overall fracture incidence of 2685/100 000 person-years was found to correspond to an incidence of 1940/100 000 and 3250/100 000 in men and women, respectively. Residual lifetime fracture risk in a person aged 60 with average life expectancy was estimated to be 29% for men and 56% for women. Estimates of clinically apparent fracture rates, with the improved methodology in this study, were higher than those previously reported in both elderly men and women, with a marked preponderance of non-hip fractures in the 60–80 year age group.

MORBIDITY AND MORTALITY AFTER OSTEOPOROTIC FRACTURES

Several studies have estimated the one year mortality after hip fracture to be around 20% in women and 30% in men.^{28–29} All-cause mortality has also been reported to be higher in men than in women after vertebral fractures: 0.85 (95% CI 0.71 to 0.96) and 0.72 (95% CI 0.51 to 0.93) for survival in women and men, respectively.³⁰ In the Dubbo study mortality was found to be increased after all major types of osteoporotic fractures.³¹ Standardised mortality ratios were higher in men both for incident and prevalent clinically diagnosed vertebral fractures. In women the ratios were 1.6 (1.4 to 1.8) for incident and 1.8 (1.6 to 2.1) for prevalent vertebral fractures. In men, these ratios were 1.8 (1.6 to 2.0) and 3.7 (3.4 to 3.9); standardised mortality ratios were higher for men than women for all fracture types.

Little published information is available on differences in the quality of life between the sexes after osteoporotic fractures. However, in the EVOS study the associations between vertebral deformities and negative health outcomes were stronger in men than in women,^{32–33} though there may be regional differences, as suggested by an analysis of German subjects³⁴; similar observations were made by Burger *et al*.²⁵ There have also been reports of higher rates of hospitalisation and institutionalisation after osteoporotic fractures in men than in women.³⁵

Risk factors for osteoporotic fractures in men

Besides bone mineral density (BMD; see below) and age, which are major risk factors, several other independent risk factors for osteoporotic fractures in men have been identified. In the Dubbo study independent risk factors for osteoporotic fractures in a multivariate analysis,³⁶ including BMD, were quadriceps weakness (odds ratio (OR)=1.43 (1.18 to 1.73) per 10 kilogram) and higher body sway (OR=1.25 (1.07 to 1.45) per 5.15 cm). Other independent risk factors were falls in the previous 12 months, a history of fracture in the previous five years, a lower body weight, and lower body height; protective factors included the use of thiazides, higher physical activity, and moderate alcohol intake.

Nyquist and coworkers showed that the risk of any fracture increases by a factor of 1.7 for 1SD decrease in skinfold thickness, measured on the dorsum of the hand.³⁷ In the NHANES

I epidemiological follow up study for hip fracture in white men,³⁸ the adjusted relative risk (RR) of hip fracture was significantly associated with presence of one or more chronic conditions (RR=1.91; 95% CI 1.19 to 3.06), 10% or more weight loss from maximum (RR=2.27; 1.13 to 4.59), and 1SD change in phalangeal bone density (RR=1.73; 1.11 to 2.68).

Poor and coworkers found that after adjusting for age, obesity, and inactivity, disorders linked with secondary osteoporosis were associated with a twofold increase in the risk of hip fracture in men (OR=2.93; 1.3 to 4.3), while conditions linked with an increased risk of falling were associated with an almost sevenfold increase in risk (OR=6.9; 3.3 to 14.8).³⁹ These factors together seem to account for about 72% of the hip fractures in men.

In a case-control study, Grisso *et al* found the following risk factors for a first hip fracture: low body mass (RR=3.8; 95% CI 2.3 to 6.4 for men in the lower quintile); premorbid leg dysfunction (RR=3.4; 2.1 to 5.4); use of cimetidine (RR=2.5; 1.4 to 4.6); use of psychotropic drugs (RR=2.2; 1.4 to 3.3); smoking cigarettes or a pipe (independent of body mass); while previous physical activity was markedly protective.⁴⁰ In a Japanese study the risk of hip fracture in a large cohort of men was increased by a low body mass index (BMI), regular alcohol intake, and prevalent fractures.⁴¹ In a large prospective study alcohol intake of more than 27 drinks a week, but not moderate alcohol intake, was associated with a significant risk for hip fracture⁴². The prevalence of falls in men aged over 65 is half that in women (19% *v* 34%), but no sex-specific factors predisposing to the differing incidence have yet been clearly identified.^{36 40}

In the MEDOS study both men and women from southern Europe were studied.⁴³ Significant risk factors for hip fracture in men by univariate analysis included low body mass index, low sunlight exposure, a low degree of physical activity, low consumption of milk and cheese, and a poor mental score. Comorbidity factors, including sleep disturbances, loss of weight, impaired mental status, and poor appetite, were also significant risk factors. Previous stroke with hemiplegia, prior fragility fractures, senile dementia, alcoholism, and gastrectomy were also associated with significant risk, whereas osteoarthritis, nephrolithiasis, and myocardial infarction were associated with lower risks. Taking drugs was not associated with a difference in risk, apart from a protective effect with the use of analgetics, independent of co-existing osteoarthritis, and an increased risk with the use of anti-epileptic agents. Of the potentially "reversible" risk factors, BMI, leisure exercise, exposure to sunlight, and consumption of tea, alcohol, and tobacco remained independent risk factors after multivariate analysis, accounting for 54% of hip fractures. Excluding BMI, 46% of fractures could be explained on the basis of the risk factors sought. Of the remaining factors, low exposure to sunlight and decreased physical activity accounted for the highest attributable

risks (14% and 9%, respectively). The use of risk factors to predict hip fractures had relatively low sensitivity and specificity (59.6% and 61.0%, respectively). It was concluded that lifestyle factors are associated with significant differences in the risk of hip fracture. Potentially modifiable risk factors, including a low degree of physical exercise and a low BMI, account for a large component of the total risk.⁴³ In the MEDOS study the pattern of risk factors for hip fracture was similar in both sexes.⁴⁴ In case-control studies, testosterone deficiency has been identified as a specific risk factor for hip fractures in men.⁴⁵⁻⁴⁷

Slight but significant declines in 25-hydroxycholecalciferol and increases in parathyroid hormone have been linked to bone loss in aging men⁴⁸⁻⁵⁰ and hypovitaminosis D identified as a risk factor for hip fracture.⁴⁷

It has been suggested that secondary causes of osteoporosis may more often play a part in symptomatic vertebral fractures in men than in women (50% *v* 35%).⁵¹ Long term glucocorticoid use, hypogonadism, alcoholism, and transplantation are well established causes of secondary osteoporosis in men and there is also some evidence for a role of gastrointestinal disorders, hyperparathyroidism, hypercalciuria, thyrotoxicosis, immobilisation, and use of anti-convulsant drugs as minor causes of secondary osteoporosis in men.⁵¹

An Sp1 binding site polymorphism in the COL1A1 gene has been shown to predict osteoporotic fractures in both men and women (RR=2.04 and 1.37 in men and women, respectively).⁵²

Role of sex hormone deficiency in age related bone loss in men

The sex differences that underlie the lower incidence of osteoporotic fractures in men may include the greater accumulation of skeletal bone mass during growth and the larger bone size in men as well as a lesser propensity to fall in elderly men. The absence of a distinctive equivalent of the menopause, with its related increase of bone turnover and accelerated bone loss resulting from oestrogen withdrawal, presumably also has a significant role.

In men, as is the case in women, acquired sex steroid deficiency results in increased bone turnover and accelerated bone loss,^{53 54} bone turnover being reduced by treatment with antiresorptive drugs.⁵³ Aging in men is characterised by a progressive decline of free (or bioavailable) serum testosterone levels (by about 50% between the ages of 25 and 75) and a progressive decline of free (or bioavailable) oestradiol levels.⁵⁵⁻⁵⁷ Results of cross sectional studies on the role of serum testosterone as an independent determinant of bone mass in elderly men have not been unequivocal,⁵⁸ yet several studies have reported a significant independent contribution of serum testosterone in the determination of cancellous⁵⁹ or cortical bone mass, or both.^{60 61} Bone turnover tends to increase both in elderly women and men, though is more pronounced in the former.^{50 62}

Interestingly, recent findings suggest that elderly women with lower serum oestrogen

levels have lower bone density values and a higher prevalence of vertebral deformities,⁶³ while several reports indicate that serum oestradiol may also be a determinant of bone turnover and bone density in elderly men.^{61 62 64} Low oestradiol levels have also been reported in men with idiopathic osteoporosis.⁶⁵ Both oestrogen resistance⁶⁶ and aromatase deficiency⁶⁷ have been associated with low bone density in men, and it has been proposed that oestrogen deficiency may be a common and relevant pathophysiological mechanism in female and male osteoporosis.⁶⁸

Giving testosterone to adult men with acquired hypogonadism has been reported to reduce bone turnover and increase bone density,^{69 70} but this needs to be confirmed in controlled trials. It has recently been reported that testosterone treatment in elderly men with moderately low serum testosterone may result in a modest increase of bone mineral density at several measurement sites.⁷¹⁻⁷³ Oestrogen treatment has been noted to increase bone mass in a man with aromatase deficiency.⁶⁷

Rate of bone loss in men

Overall, the rate of bone loss at cortical sites seems to be greater in women than in men, whereas the rate of trabecular bone loss is less clearly influenced by sex. Mazess *et al* observed almost identical rates of trabecular bone loss in both sexes.⁷⁴ Data from longitudinal studies⁷⁵⁻⁷⁸ have consistently shown that the rate of cortical bone loss in men may be considerably more rapid (0.5–1% a year) than estimated from cross sectional studies (0.1–0.3% a year).^{74 79 80} In the cross sectional Framingham Osteoporosis Study the rate of bone loss at the predominantly trabecular trochanter site was similar in men and women (0.45% and 0.53% a year, respectively).⁷⁹ In the longitudinal Dubbo study⁷ a higher rate of bone loss at the femoral neck was found, with increased rate of bone loss in the more elderly and rather similar rates of bone loss in both sexes: 0.96% a year (95% CI 0.64 to 1.28%) in women and 0.82% a year (0.52 to 1.12%) in men. In the Rotterdam study the rate of bone loss, adjusted for age and body mass index, was 0.0025 and 0.0045 g/cm²/y in men and women, respectively.⁸¹ Bone loss accelerated with age, as was seen more clearly in men than in women. Lower body mass index and cigarette smoking were associated with increased bone loss in both men and women. In men, higher calcium intake was associated with lower rates, and disability was associated with a tendency to higher rates of bone loss. Alcohol intake was inconsistently related to the rate of bone loss in both sexes.

It should, however, be pointed out that age related changes in bone mineral density are accompanied by some sex-specific changes in bone geometry, with a higher increase of the cross sectional area of bones with advancing age in men.^{82 83} Nevertheless, in longitudinal follow up continuing subperiosteal expansion seems to be similar in both sexes.⁸⁴

Not only the cross sectional area of long bones but also the size of the vertebral bodies is

clearly larger (by 25%) in men than in women.⁸⁵ Prevalent areal BMD in adult men is higher than in adult women. However, sex differences in bone density are usually no longer apparent when volumetric densities are being considered.⁸⁶ Owing to the sex differences in areal BMD, the prevalence of osteoporosis according to the proposed diagnostic categories of the WHO (World Health Organisation;⁸⁷) will be different between the sexes.⁸⁸

Relation between prevalent bone mineral density and fracture risk in men

A working party of the WHO has formulated proposals for diagnostic categories in osteoporosis⁸⁷ based on the relation between BMD (expressed as a T score—that is, BMD of the subject expressed as units of SD difference from the mean BMD in young adults) and the prospectively evaluated fracture risk. However, these proposals of the WHO working party apply only to white postmenopausal women.

Recently, prospective data on the relation between areal BMD and fracture risk in men became available. Gärdsell *et al* reported that bone mineral content at the forearm corrected for bone width is predictive of future fragility fractures.⁸⁹ Other significant risk factors in this study were falls, lower grip strength, and lower body weight, as well as a history of previous vertebral fracture or cerebral disorder. Several cross sectional studies have observed lower bone mineral densities in men with prevalent fracture.⁹⁰⁻⁹⁵ In these latter studies, threshold BMD values for fractures seemed to be somewhat higher in men than in women. Men with only non-fragility fractures had no difference in BMD than men without fractures.

In the Hawaii osteoporosis study^{96 97} a relation was found between low BMD and vertebral fracture risk. Bone density was a significant predictor of vertebral fractures in both men and women. The risk of having a new fracture during follow up increased by 1.5 to 2.0 times for each 1SD decrease in baseline BMD for both women and men, depending on the BMD measurement site. When the incidence of new fractures was examined as a function of calcaneus BMD, men and women had equivalent risks of fracture for a given level of BMD. Similar results were found for the distal and proximal radius BMD measurements. In contrast with BMD, there were substantial differences in fracture risks between men and women at similar levels of bone mineral content (BMC; that is, total bone mineral content in the region of interest; BMD is BMC divided by the projected area of the measurement site). Adjusting for body size reduced the differences between men and women for BMC, with results similar to those for BMD. In the Rotterdam study hip fracture incidence was found to be related to BMD in both women and men.⁹⁸ The relative risk was 2.5 for each SD decrease in femoral neck BMD (1.8–3.6) in women, while this relative risk was 3.0 (1.7–5.4) in men. These relative risks were not statistically different. The relation between baseline BMD and hip fracture risk is similar in

men and women, while the average BMD is higher in men than in women at every given age, and the decrease of BMD with age is slower in men. For a given absolute hip areal BMD value, hip fracture risk is similar in both sexes.

The association between changes in BMD and fracture risk was also evaluated in the Hawaii osteoporosis study.⁹⁷ For these analyses, rates of changes in BMD were calculated up to the end of follow up or the time of the first fracture (whichever came first). Adjusting for bone loss rate did not alter the association between BMD and fracture risk. Changes in BMC and BMD were significant predictors of new vertebral fractures after adjusting for bone density, indicating that bone density and bone loss rate both contribute independently to fracture risk. The results indicate that fast decline in bone density is associated with an increased risk of subsequent fractures. Although the magnitude of this effect was comparable for men and women, it did not attain statistical significance for men, possibly because the sample size for men was smaller.

Although the limited data available are not unequivocal, more recent studies seem to indicate that values for the biochemical markers of bone turnover do tend to increase in aging men and that there is a negative association between the level of bone turnover and prevalent bone mineral density in men, as is also the case in women.^{50 62} To date there are no published data on the independent contribution of bone turnover on fracture risk in men.

In men with hypogonadism severe deterioration of the parameters of trabecular connectivity was described as the most striking finding.⁹⁹ In 108 men with osteoporosis (62 with vertebral fractures) the correlations between trabecular bone volume and microarchitectural parameters are logarithmic or exponential; after adjustment for age, body mass index and femoral BMD, the risk of vertebral fracture seems to be significantly related to changes of trabecular connectivity.¹⁰⁰

Johansson and coworkers have reported that prevalent bone mineral density is a predictor of survival both in men and women.¹⁰¹ A decrease of 1SD of BMD in a univariate analysis was associated with a 1.39-fold increase in mortality in both men (95% CI 1.25 to 1.56) and women (95% CI 1.22 to 1.58), and a multivariate analysis showed a relative risk of 1.23 (95% CI 1.10 to 1.41) in men and 1.19 (1.02 to 1.39) in women. All relations were adjusted for sex, age, and follow up. This study indicates that BMD is a predictor of survival, especially for subjects over 70; bone mineral density was found to be a better predictor of imminent death than blood pressure and cholesterol. Similar findings were reported from the Rotterdam study.¹⁰²

Treatment-induced changes in bone density and fracture risk

At present, no controlled data on the effect of changes in bone mineral density or bone turnover induced by pharmacological intervention, on the resulting fracture rate in men with

primary osteoporosis, have been published as a full paper. Preliminary data on a prospective controlled trial of 146 osteoporotic men treated with alendronate and 95 subjects treated with placebo have been reported,¹⁰³ which indicate that increased BMD during antiresorptive treatment is associated with a (non-significant) trend towards reduced risk for vertebral fracture, similar to the findings in women. In a small scale study Ringe *et al* found an increased vertebral BMD and reduced rate of vertebral fracture during treatment with monofluorophosphate.¹⁰⁴

In women, large well controlled prospective studies have shown that antiresorptive drugs can effectively reduce fracture risk in osteoporotic patients.¹⁰⁵⁻¹¹⁰ Among these trials the observed changes in BMD, reduction of fracture risk, and the relation between them vary, possibly owing to differences in inclusion criteria and measurement technique and/or the pharmacological properties of the drugs. In some of these studies it has been documented that the anti-fracture efficacy is limited essentially to those subjects with initially low bone mass (osteoporotic according to the WHO diagnostic criteria).^{106 111} In the Fracture Intervention Trial, larger increases in BMD during alendronate treatment were associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis.¹¹²

Comparison of treatment-induced changes in BMD and fracture rates between these studies in postmenopausal women is hazardous owing to the differences in inclusion criteria. Nevertheless, in a meta-analysis Black *et al* analysed the results of 13 clinical trials including alendronate, calcitonin, oestradiol, etidronate, raloxifene, risedronate, and tiludronate to determine the extent to which improvement in spine BMD is related to reduction in vertebral fracture incidence.¹¹³ Trials were included that had at least five incident fractures for each treatment group, lasted for at least two years, and reported changes both in spine BMD and rates of vertebral fractures. Within the range of differences in spine BMD noted in these trials (1 to 8%), each 1% improvement in spine BMD corresponded with a 3.3% (95% CI 1.0 to 5.6%) reduction in fracture risk obtained during treatment. Other factors, such as prevalent rate of bone remodelling¹¹⁴ or tissue architecture, may also be important. In this regard, it can be mentioned that in studies with anti-resorptive drugs increases in BMD are consistently associated with a decreased rate of bone turnover, which in turn can be expected to have favourable effects on the preservation of bone tissue architecture.

Summary and conclusions

In summary, the at least twofold higher incidence of osteoporotic fractures in women than in men seems to result from quantitative differences in risk factors, rather than from different risk factors (for example, higher BMD, higher BMI, lower rates of falls, etc) Other factors that may contribute to the differences in fracture incidence are the differences in bone geometry with greater bone size in men and the

more progressive pattern of changes in sex steroid exposure in men than in women. An important factor to be considered is, of course, the shorter life expectancy of men.

Notwithstanding the existing differences in pathophysiology of osteoporosis between sexes and the difference in age-specific incidence of osteoporotic fractures, recent insights also suggest important similarities between osteoporosis in women and men. An important observation in this regard is that, even though there are sex differences in bone geometry, the fracture rate seems to be similar in both sexes for the same absolute areal BMD level. Furthermore, age related rates of BMD changes are similar in elderly men and women, and for both sexes there is a negative relation between bone turnover and prevalent bone mineral density in the elderly.

The main limitation for the extrapolation of treatment outcomes in women to men, is the lack of data on the effects of changes in BMD and bone turnover resulting from pharmacological interventions on fracture rates in men. However, limited information derived from recent trials in primary and glucocorticoid-induced osteoporosis indicates that similar changes in BMD do result in similar trends for changes in fracture rates in both sexes.^{103 115 116}

The data presented in this review show important points of concordance between both sexes for the relation between BMD and fracture risk in untreated populations. The remaining question is whether it is reasonable to assume that a drug having shown anti-fracture efficacy in women might also reduce fracture risk in men if similar changes in BMD have been obtained for a similar treatment regimen after two or three years of treatment.

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Appendix

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