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doi: 10.1111/joim.12366

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Osteoporosis: the emperor has no clothes

■ T. L. N. Järvinen¹, K. Michaëlsson², P. Aspenberg³ & H. Sievänen⁴

From the ¹Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland, ²Section of Orthopaedics, Department of Surgical Sciences, Uppsala University, Uppsala; ³Clinical Sciences, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden, and ⁴The UKK Institute for Health Promotion Research, Tampere, Finland

Abstract. Järvinen TLN, Michaëlsson K, Aspenberg P, Sievänen H (University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; Uppsala University, Uppsala; Linköping University, Linköping, Sweden; and The UKK Institute for Health Promotion Research, Tampere, Finland). Osteoporosis: the emperor has no clothes. (Key Symposium). *J Intern Med* 2015; **277**: 662–673.

Current prevention strategies for low-trauma fractures amongst older persons depend on the notions that fractures are mainly caused by osteoporosis (pathophysiology), that patients at high risk can be identified (screening) and that the risk is amenable to bone-targeted pharmacotherapy (treatment). However, all these three notions can be disputed.

Pathophysiology. Most fracture patients have fallen, but actually do not have osteoporosis. A high likelihood of falling, in turn, is attributable to an ageing-related decline in physical functioning and general frailty.

Screening. Currently available fracture risk prediction strategies including bone densitometry and

multifactorial prediction tools are unable to identify a large proportion of patients who will sustain a fracture, whereas many of those with a high fracture risk score will not sustain a fracture.

Treatment. The evidence for the viability of bone-targeted pharmacotherapy in preventing hip fracture and other clinical fragility fractures is mainly limited to women aged 65–80 years with osteoporosis, whereas the proof of hip fracture-preventing efficacy in women over 80 years of age and in men at all ages is meagre or absent. Further, the antihip fracture efficacy shown in clinical trials is absent in real-life studies. Many drugs for the treatment of osteoporosis have also been associated with increased risks of serious adverse events. There are also considerable uncertainties related to the efficacy of drug therapy in preventing clinical vertebral fractures, whereas the efficacy for preventing other fractures (relative risk reductions of 20–25%) remains moderate, particularly in terms of the low absolute risk reduction in fractures with this treatment.

Keywords: cost-effectiveness, osteoporosis, prediction, screening, treatment.

Introduction

The World Health Organization introduced operational diagnostic criteria for osteoporosis in 1994 [1]. Virtually every physician in the world was made aware of the notion that a decrease of 1 SD in dual-energy X-ray absorptiometry (DXA)-measured bone mineral density (BMD) doubles the risk of osteoporotic fractures. To manage this challenge of osteoporosis effectively, diagnosis of osteoporosis and prevention of related fractures were simplified for physicians. A widely promoted consensus depended on the following: (i) osteoporosis (defined as BMD T-score ≤ -2.5) is the main cause of low-energy fractures in ageing populations, (ii) bone densitometry (DXA) reliably identifies individuals at risk of these fractures and (iii) these fractures can be cost-effectively prevented by bone-targeted

pharmacotherapy. Accordingly, by the end of the 20th century, many physicians were referring individuals for BMD testing and prescribing bone-targeted pharmacotherapy to millions of otherwise asymptomatic persons, on the basis of a reduced BMD value alone.

Although there is a wide consensus amongst the 'mainstay' regarding the diagnosis, screening and treatment of osteoporosis, many of the existing beliefs and concepts are indeed debatable when placed under proper scientific scrutiny. Prevention of any medical condition is naturally appealing, but it is essential to strike the right balance between benefits and harms with any intervention. In this review, we demonstrate the most obvious weaknesses in the prevailing general reasoning about osteoporosis to highlight the fact that there

is yet the possibility for improvement in our existing paradigms for osteoporosis and fracture prevention.

Pathophysiology

To what extent do fracture patients have osteoporosis?

It is well known that the relative risk of a fracture is at least quadrupled in individuals with DXA-verified osteoporosis compared to those with normal BMD [2]. However, a large population-based study of women aged 65 years or above showed that 85% of all low-trauma fractures were not attributable to osteoporosis [3]. Moreover, although BMD is, on average, associated with risk of fracture [2], the added discriminatory value of BMD to clinical risk factors remains modest [4]. In addition, the ability of BMD to predict hip fractures decreases substantially with increasing age [5]. For example, the relative risk of hip fracture increased 13-fold from 60 to 80 years of age in both men and women, whereas the age-related decline in BMD accounted only for a twofold increased risk [6]. A 44-fold rise in hip fracture incidence from 55 to 85 years of age was reported in Swedish women, for which the impact of age was 11-fold greater than that of BMD [7].

It is also well established that bone deteriorates with age, but even a weak bone can survive normal life without exceptional loading caused by a fall-induced impact (Fig. 1). Fractures are primarily caused by falls [8], including the case of vertebral fractures [9]. Thus, even asking the simple question 'Do you have impaired balance?' can predict about 40% of all hip fractures [10], whereas osteoporosis predicts <30% [3]. With regard to the distinct fracture incidence between women and men, the higher incidence in women is attributable to a higher incidence of falling, not to lower BMD [11] (Fig. 2).

The risk of falling increases with age and reduced physical function, and falls are very common amongst the older population: around one-third of generally healthy individuals aged 65 or above and a half of those aged 80 or above will fall at least once a year. However, only 5% of falls result in any fracture, and only 1% in a hip fracture [12, 13]. An important explanation for the increased risk of falling with older age is muscle weakness. This is caused not only by decreased muscle mass, but also by reduced muscle strength and power, as a consequence of loss of muscle fibres, fatty degen-

eration and fibrotic changes, and a decreased number of functioning motor units [14]. Muscle density, not only muscle size, is an important determinant of future hip fracture risk [15]. The weight of skeletal muscle comprises ~45% of the body weight at 21–30 years of age but decreases to ~27% after the age of 70. Over the adult life span, thigh muscle strength is reduced on average by 40% [16]. It is most likely that the ageing-related muscle loss and reduced balance contribute to fracture risk through increased propensity to falling. This could, at least partly, explain the relatively poor predictive value of bone loss in identifying those at risk of sustaining fractures in old age.

Is fracture risk inherited?

Numerous cross-sectional studies have consistently shown a strong heritable component of bone density, mass and turnover markers [17–19]. However, the mean heritability of bone loss [20] and fractures is modest [21, 22], especially in old age [20, 21], and the heritability of hip fractures appears to be negligible in older women and men [21]. There are several important clinical predictors of fracture risk in the elderly that are either correlated with or act independently of BMD [23]. Although the search for BMD-specific single nucleotide polymorphisms by whole-genome and whole-exome sequencing has been successful with some interesting findings [24–26], it has resulted in identification of only a small fraction of the genetic variants responsible for regulation of BMD and susceptibility to fracture. Variation in these genes accounts for only 6% of the BMD variation, and even less of the variance in fracture occurrence [27].

What is the explanation for the apparent discrepancy between the strong heritability of bone traits in cross-sectional studies and the low heritability of fracture risk? As noted above, fractures are mainly caused by falling [8] and the genetic liability of impaired balance (propensity to falling) is modest [28, 29], at best. Accordingly, it is highly unlikely that genetic tests will substantially improve the identification of individuals at high risk of fractures, especially at older age. The mean age of hip fracture patients in Europe is about 80 years, and over 75% of all hip fractures occur amongst individuals older than 75 years [30]. Therefore, given the low heritability of bone loss and fractures in old age, a likely explanation of the

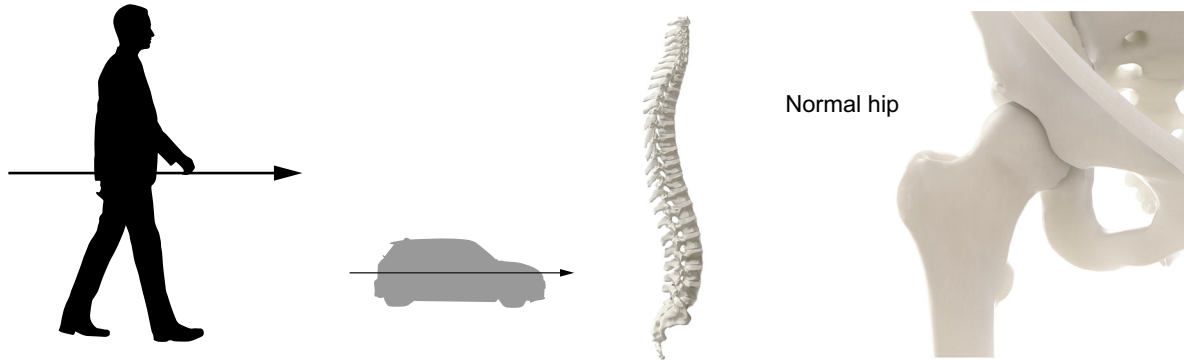
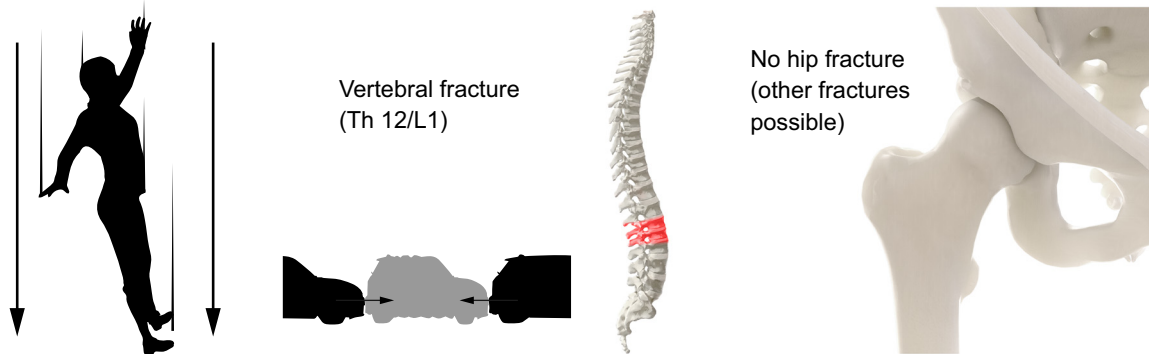
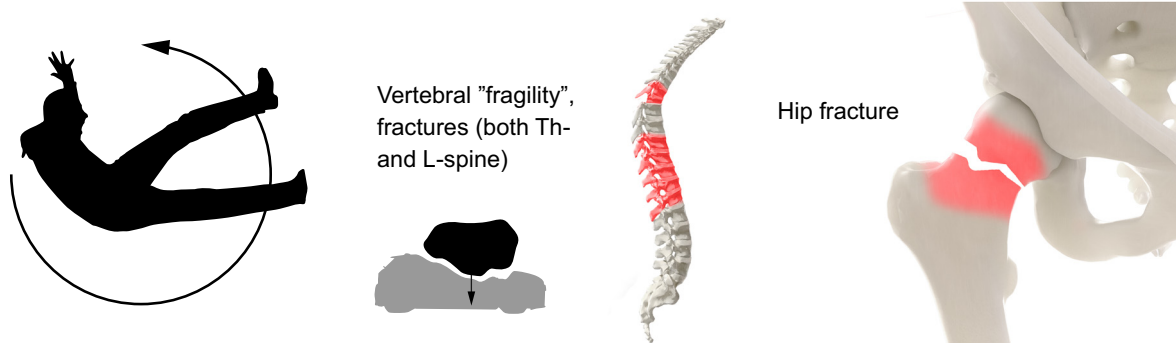
(a) Normal loading**(b) Accidental loading, Habitual direction****(c) Accidental loading, abnormal direction**

Fig. 1 How is structural damage/fractures related to the design of cars/the skeleton? (a) Cars are designed to run on their wheels. In terms of safety, the design of cars is optimized to keep the driver and passengers intact during collisions from the typical directions of impact (i.e. the front or rear). However, a similar or even smaller force can cause profound damage if it comes from an atypical (unforeseen) direction. (b) By analogy, the human skeleton is adapted to bipedal gait and the resulting habitual locomotive loadings. The skeleton has a high capacity to resist fractures when a trauma leads to exaggerated forces with an orientation similar to habitual activities. (c) However, in the majority of fractures in older adults, the trauma caused loading of the skeleton in a direction, rate and magnitude that it was not adapted to. Examples of such loading incidents are lifting a shopping bag with straight knees (causes vertebral fractures) and a sideways fall directly onto the hip (the main cause of hip fractures). Adapted from [105].

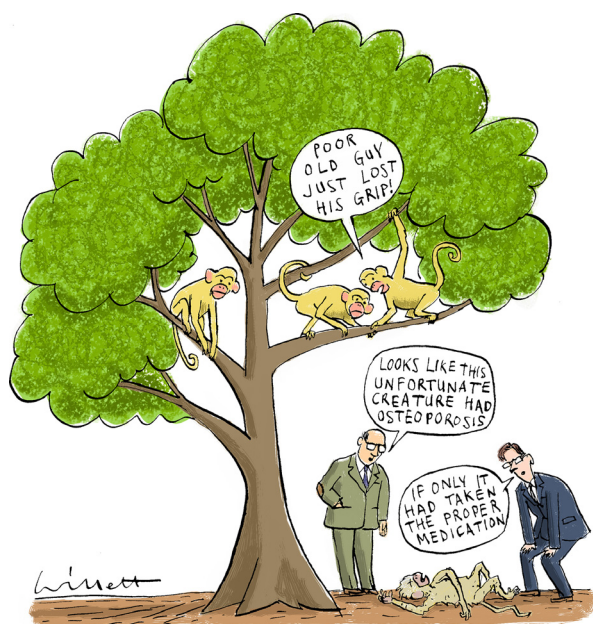


Fig. 2 Fractures are primarily due to falling, not osteoporosis. Despite a wide consensus that fractures in adults are ‘osteoporotic’, evidence indisputably shows that both hip and vertebral fractures are predominantly traumatic (caused by an injury).

low genetic contribution to fractures in large genomewide association studies is the dominance of environmental and lifestyle influence on this complex phenotypic trait.

Are vertebral fractures truly osteoporotic?

Vertebral fractures are commonly considered to be equally important to those of the hip [31]. However, the diagnosis of vertebral fracture is quite arbitrary; depending on the criteria used for classifying a change in an X-ray image as a fracture, the prevalence of vertebral fractures can vary by as much as 3% to 90% in a given elderly population [32]. Moreover, a symptomatic vertebral fracture is rarely ‘spontaneous’ or purely osteoporotic; at least 50% are trauma induced and, in particular, are due to falling on the buttocks or lifting an object with straight knees [33–35]. In a recent survey of vertebral fracture-related emergency department visits and hospitalizations in the elderly Dutch population, 83% of vertebral fractures were caused by a low-energy fall incident [36]. Seemingly benign physical activities, such as bending or lifting light objects, produce relatively large loads on the spinal

column (up to 10 times higher compared with perfect posture) and are capable of fracturing a vertebra [35, 37] (Fig. 1). Only one-third of the X-ray changes termed vertebral fractures are symptomatic [38], and the occurrence of vertebral fractures poorly predicts either the existence of back pain or the functional status of the spine [39, 40].

Although it is commonly argued that vertebral fractures increase the risk of death, it should be noted that almost every illness in older adults, by virtue of the definition of the word ‘illness’ as an indicator of frailty and weakness, is related to increased morbidity and mortality, but is seldom a truly independent risk factor or direct cause of death. Accordingly, the more relevant question is, how much of the increased *morbidity and mortality* risk associated with vertebral fractures can be reduced by bone-targeted pharmacotherapy? As demonstrated herein, there is no evidence that pharmacotherapy would either provide a clinically relevant reduction in vertebral fractures or reduce the related mortality risk (see below).

Do fractures cause excess mortality?

One of the most common arguments for screening and treatment of osteoporosis is that fractures cause excess mortality, and therefore, bone-targeted pharmacotherapy could improve survival [41]. However, evidence supporting this notion is scarce. Michaelsson *et al.* [42] recently estimated the excess mortality associated with a hip fracture event, controlling for genetic constitution, comorbidities, shared familial environmental factors and lifestyle through following identical twin pairs discordant for hip fracture. In younger men (<75 years of age) and in women, irrespective of age, the excess risk of mortality lasted only during the first year after the hip fracture event. The analysis indicated a more long-lasting impact of hip fracture on subsequent mortality risk only in men above 75 years of age. This is a strong indication that the excess mortality after a hip fracture in women, including duration of the excess risk, has been overestimated in previous studies with ordinary designs [43].

The most convincing evidence suggesting that bone-targeted pharmacotherapy could have an effect on mortality comes from the HORIZON trial [44], but the results have been questioned [45]. In a multivariable analysis of the HORIZON data adjusted for relevant risk factors (subsequent frac-

ture, change in BMD, infections, cardiovascular events, arrhythmias and falls), zoledronic acid was shown to reduce the risk of death by 25% [46]. Although subsequent fractures were associated with death, they merely explained 8% of the zoledronic acid effect on mortality. Further, adjustment of the data for acute (nonfatal) events occurring during follow-up eliminated the death benefit and established an unexpected association: the protective effect against arrhythmias was apparent in the secondary prevention arm of the HORIZON trial, whereas the incidence of arrhythmias was paradoxically increased amongst the zoledronic acid-treated group in the primary prevention arm [46].

Screening

Is BMD an adequate surrogate of individual bone fragility?

Dual-energy X-ray absorptiometry-measured BMD is strongly correlated with bone strength, and the relative risk of future fractures is increased by low BMD or osteoporosis at the group level or in a population; however, this epidemiological association has little clinical relevance for the individual. Although BMD as a predictor of future fracture risk is well established and several prospective studies have demonstrated a 1.5- to 2.5-fold increased risk of fracture for every 1 SD decrease in BMD [2, 3, 5], BMD alone displays poor sensitivity in predicting future fractures. Fewer than one in three hip fractures are attributable to osteoporosis as defined by total hip BMD [3]. Thus, sufficiently accurate identification of fracture-prone *individuals* is not possible on the basis of DXA-defined osteoporosis. Moreover, the ability of BMD to predict hip fractures declines with age: at 50 years of age, the gradient of risk (the relative risk per 1 SD decrease in BMD) is almost four, whereas at the age of 85, it is <2 [5]. Only relative risk values of at least three (corresponding to an area under the receiving operator characteristic (ROC) curve of about ≥ 0.8) are considered to be of clinical relevance for an individual risk assessment [47].

Further, the DXA measurement inherently assumes that the scanned body region (e.g. hip or lumbar spine) comprises only bone and homogeneous soft tissue components, but it is clear that this two-component simplification conflicts with clinical reality (individual anatomy and body composition), resulting in substantial inaccuracy of individual measurement (Fig. 3a). Despite the fact that DXA measurements are highly repeatable, the

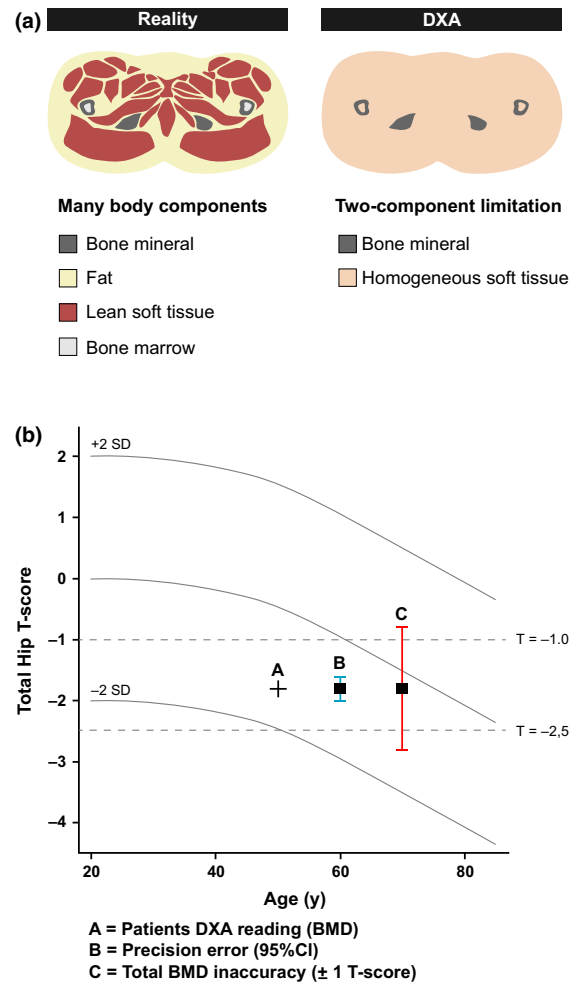


Fig. 3 Inherent inaccuracy related to dual-energy X-ray absorptiometry (DXA)-derived bone mineral density (BMD) seriously undermines the method. (a) The three body components of bone mineral, fat and lean soft tissue have different attenuation coefficients, but DXA employs two photon energies and can thus only resolve two components at a time. Therefore, assumptions are made with DXA about fat versus lean tissue ratios in the calculation of BMD. Numerous studies (using both phantoms and cadaver specimens) have consistently shown that the magnitude of uncertainty inherent in BMD measurement can be ± 1 T-score. (b) To illustrate the difference between repeatability (precision error) and accuracy (error), the black cross shows a patient's result plotted on a typical DXA scan report. The blue error bars denote the same T-score result drawn with an error bar indicating the 95% confidence interval (CI) of ± 0.2 in the T-score assessment arising from BMD precision errors. Finally, the same result is drawn with an error bar indicating the 95% CI of ± 1.0 in the T-score assessment arising when accuracy errors and precision errors are combined. Adapted from [49].

measurement accuracy is important with regard to estimated bone strength. The inherent uncertainty in the BMD measurement can correspond to one T-score unit to either direction or even more [48–50]. For example, a measured T-score of -2.5 (indicating osteoporosis) can reflect a true T-score of between -3.5 (clear osteoporosis) and -1.5 (slight osteopenia) without any possibility of knowing the true value for the given individual (Fig. 3b). Therefore, even large individual changes in BMD, corresponding to those typically observed in clinical trials, may become irrelevant in terms of fracture prediction [51].

Are fracture prediction tools useful for an individual risk assessment?

Extensive attempts have been made to identify high-risk individuals and validate clinical risk factors, either alone or in combination with BMD [52]. Similar to the Framingham Risk Score and the Systematic Coronary Risk Evaluation (SCORE) tool for predicting an individual's susceptibility to cardiovascular disease, these tools (e.g. Garvan, QFracture and FRAX[®]) typically combine age and sex with clinical risk factors to provide an estimate of the 5- or 10-year probability of fracture for an individual. A clear advantage of fracture prediction tools is that they provide an estimate of absolute risk; therefore, even if a 55-year-old woman has osteoporosis according to DXA, she can still have a low 10-year risk of fracture that might not indicate the need for pharmacological treatment.

Of the many available tools, the most widely used is the FRAX[®] tool [53, 54]; on average, it has 8000 users each day. However, the method has been criticized for flaws in design and performance [55], integration of mortality risk [56, 57] and lack of transparency [58]. Concern has also been expressed regarding the possibility that these tools promote overdiagnosis. For example, if the FRAX[®]-based guidelines were applied, at least 72% of white women >65 years and 93% of those >75 years in the USA would be recommended for drug therapy [59]. For comparison, using the BMD-based diagnosis of osteoporosis (the current trigger for drug treatment) the corresponding values for the EU are 34% and 43%, respectively [30]. Accordingly, using the new National Osteoporosis Foundation (NOF) guidelines leads to an approximate doubling of the population for which drug treatment is recommended. The UK-based National Osteoporosis Guideline Group (NOGG) guidelines similarly promote overtreatment, but through a

different mechanism. The NOGG guidelines, incorporated into the FRAX[®] UK risk tool, advocate pharmaceutical intervention in individuals whose estimated fracture risk exceeds that of an individual of the same age and gender with a prevalent fragility fracture. Paradoxically, this leads to advocacy of drug treatment for younger individuals whose absolute risk of fracture is quite low, yet not for older individuals with higher absolute risk. In short, FRAX[®]-based screening and subsequent treatment recommendations promote overdiagnosis and misdirection of pharmaceutical resources (Fig. 4).

Despite these concerns, the use of a 'high-risk' identification strategy through fracture risk assessment tools is also recommended by many national guidelines, including the FRAX[®] in the National Osteoporosis Foundation (NOF) [60], the NOGG [61], Osteoporosis Canada [62] and the UK National Institute for Health and Care Excellence (NICE) [63]. Against this background, it is noteworthy that, to our knowledge, the effect of these tools in selecting patients for therapy and thus



Fig. 4 Fracture risk prediction tools seem to expand the treatment thresholds. Whatever the FRAX[®] score for a given patient, the outcome is almost always the same: drug therapy.

improving fracture outcomes has not been determined to date. Efficacy studies of bone-specific drugs have largely been undertaken in individuals with low BMD and previous fractures. It thus remains uncertain whether the treatment is as effective when prescribed on the basis of clinical risk factors and related risk assessment. For example, the antifracture efficacy of risedronate could not be demonstrated in women over the age of 80 who were selected primarily on the basis of their risk of falling [64]. Neither is there proof from pharmaceutical interventions that fracture risk would actually be reduced in those with a high FRAX[®] score, and whether FRAX[®] in daily practice improves decision-making and, ultimately, patient-important outcomes remains unproven [65]. A recent re-analysis of the data from the large Fracture Intervention Trial (FIT) showed no significant association between FRAX[®] score and reduction in fractures by alendronate [66]. In summary, the utility of fracture prediction tools for selecting individuals for bone protective treatment needs to be confirmed before their widespread use can be recommended [63].

Treatment

Evidence-based medicine relies to a large extent on results from RCTs, and many of the problems in any clinical field are related to judging the extent to which findings under well-controlled circumstances apply to ordinary healthcare settings.

Does the existing evidence justify wide-scale use of bone-targeted pharmacotherapy?

Benefits of any medical intervention should be evaluated within the context of the three-step hierarchy of research evidence originally defined by Archie Cochrane: efficacy, effectiveness and cost-effectiveness [67, 68]. Basically, the strategy to prevent fractures by bone-targeted pharmacotherapy would be acceptable if the drugs were cheap, effective and with low risk of associated harms. However, it is questionable whether current medications meet these requirements.

With regard to the costs and effectiveness, even under the idealized circumstances of *efficacy* trials, we found that less than a half of all fractures could be prevented, whilst the cost of averting one hip fracture was about £100 000 [68]. By contrast, the average total cost of treating one hip fracture patient over the first year after fracture is about £16 000

[68]. Further, despite the fact that the mean age of hip fracture patients in Europe is about 80 years, and more than three in four hip fractures occur amongst individuals older than 75 years [30], this age group is under-represented in or even absent from most clinical trials assessing the antihip fracture efficacy of preventive pharmacotherapy. Only three of the 33 RCTs published so far have included a sufficient number of women over 75 years of age to allow analysis of hip fracture incidence [44, 64, 69], and these three studies did not show significant efficacy in this age group. Nevertheless, it is commonly believed that bisphosphonates can reduce the relative fracture risk independent of age, so that the absolute risk reduction would increase with age or baseline risk [70–72]. Similar to those for other 'risk diseases' [73], most osteoporosis guidelines ignore the lack of evidence in the oldest old (>80 years of age) and extrapolate the efficacy estimates derived from younger adults to this group. It is unlikely that the oldest old are comparable to those in their 60s or 70s in terms of their response to drug therapy. Finally, osteoporosis is primarily considered to be a female disease, but about 30–40% of hip fractures occur in elderly men [30]. However, there is a dire lack of available evidence regarding hip fracture prevention in men.

Is there any *real-life* evidence? Whilst confounding by indication is an obvious risk in these studies, they actually provide pertinent evidence about the feasibility of using bone-modifying drugs to prevent fractures. However, existing real-life data do not support clear clinically relevant antifracture (including hip fracture) effects of bisphosphonates or any other compounds [74–80]. For example, in a recent Canadian study it was found that despite greater than fourfold differences between provinces in prescribing rates of osteoporosis medication in those aged >55, there were still no between-province differences in hip fracture rates in either gender or any age group [80]. It is arguable that this effectiveness evidence, despite being based on 40 000–210 000 bisphosphonate users in each province, lacks adequate power because of heterogeneous populations (e.g. in terms of age, socioeconomic status and comorbidities). However, the clinical relevance of such a marginal fracture reduction effect, if present, can be disputed.

What about the evidence regarding bone-targeted pharmacotherapy for prevention of vertebral fractures? It is commonly claimed that treatment of osteoporosis can reduce vertebral fracture rates by

30–70%. These are the highest relative risk reductions achieved by pharmacotherapy for the various types of fractures amongst older adults. However, there are considerable uncertainties related to the quality of evidence on the efficacy of bone-targeted pharmacotherapy in preventing vertebral fractures [81]. In a recent systematic review of the entire bisphosphonates evidence base, the authors identified 33 sufficiently long (≥ 1 year) RCTs to assess the efficacy of bisphosphonates on vertebral fracture incidence amongst postmenopausal women [81]. However, only two of these trials [82, 83] reported data on *symptomatic* vertebral fracture in the primary prevention setting, showing a 44% relative reduction [95% confidence interval (CI) 21–60]. In the secondary prevention setting, a 54% relative reduction (95% CI 25–72) was observed, but this was also based on only two trials comparing alendronate to placebo [84, 85]. Of note, the authors concluded that these efficacy estimates were likely to be inflated due to substantial attrition bias from incomplete follow-up and outcome assessment. Moreover, the evidence derived from efficacy trials (because of carefully selected patient populations) poorly represents the real-life clinical setting [68].

Osteoporosis guidelines systematically ignore the obvious ‘evidence void’ in the RCTs (i.e. no antihyperfracture evidence for women under 65 or above 80 years, or for men in general) and instead extrapolate efficacy estimates derived from younger women to their older counterparts and even to men. Assertions by NOF and NOGG on the ‘cost-effectiveness’ of bone-targeted pharmacotherapy are not based on actual trials, but on a computer-modelled cost-effectiveness analysis [70] which assumes that bisphosphonates achieve a constant relative risk reduction for fractures irrespective of age, sex and baseline risk of fracture (or individual bisphosphonate). Accordingly, the model predicts a highly favourable (steadily increasing) absolute risk reduction with age and baseline risk, which is hardly the case as outlined above.

Is bone-targeted pharmacotherapy safe?

Bone-targeted pharmacotherapy, like any medication, is not without associated risks. Considerable adverse effects of bone-targeted drugs have become evident. The first reports of atypical femoral shaft fractures in bisphosphonate users after minimal or no trauma were published in 2005 [86], but it took almost 10 years to finally establish the causal

association between oral bisphosphonate use and atypical femoral fractures [87]. For an association to be regarded as causative, it has to be strong, show a dose- or time-dependent relation, cease with the end of treatment and have a plausible pathophysiological explanation. In the case of bisphosphonate use and atypical fractures, all these requirements are fulfilled. Comorbidities and concomitant use of other drugs do not seem to explain the association. Genetic predisposition for atypical fractures is, however, still a possible explanatory factor. Nonetheless, the association between bisphosphonate treatment and atypical femoral fractures has now been shown in several observational studies with similar methodologies. Conflicting results in some studies are largely attributable to differences in the radiographic definition of atypical fractures [88, 89] and lack of statistical power [90]. Despite the strong and apparent causative association between bisphosphonates and atypical fractures, about 20% of patients with an accurately defined atypical femoral fracture have never been treated with bisphosphonates. In this context, the long-disputed [91] relation between smoking and lung cancer is pertinent. Smoking, the main established cause of small cell and nonsmall cell lung cancer, contributes to 80% and 90% of lung cancer deaths in women and men, respectively [92], whilst the remaining 10–20% of cases are not attributable to smoking. Amongst heavy long-term smokers, men are 23 times more likely to develop lung cancer and women are 13 times more likely, compared to never smokers [92]. Nonetheless, RCTs of smoking cessation have shown no benefit on mortality [93]. The current evidence for the link between bisphosphonates and atypical fractures has striking similarities although nowadays the fact that smoking is a cause of lung cancer and premature death would not be disputed.

According to the most recent data, the relative risk of atypical fracture after a few years of bisphosphonate use (RR >100) is higher than that for lung cancer amongst smokers, although the absolute risk is modest: 11 atypical femoral fractures per year amongst 10 000 users of bisphosphonates [94]. One atypical femoral fracture will occur for about 300 patients treated for 3 years. Based on these real-life estimates of risks related to the use of bone-targeted pharmacotherapy, it has been argued that the off-label use of these drugs might reverse the fracture-preventive benefit, leading instead to a dominance of adverse events, when

the net effect on the entire population is considered [95].

Conclusion

Is osteoporosis different from other risk diseases?

Advocates of the prevailing osteoporosis-based prevention and treatment strategy for fractures argue that BMD predicts fracture risk as accurately as blood pressure predicts stroke and considerably better than serum cholesterol predicts coronary artery disease [2, 96, 97]. This is true. However, it is rarely noted that this strategy also leads to labelling the majority of otherwise asymptomatic older people as sick and subjecting them to long-term medication to prevent relatively rare morbid events (Fig. 4).

A disease label can have both positive and negative consequences [98, 99], but, as stated by Spence, 'labels are sticky and peeling them off can be a messy business' [100]. In a survey of a random sample of 261 women who had undergone bone densitometry, Rubin and Cummings [101] assessed how the results of bone densitometry affected the women's decisions about measures to prevent fractures. They also determined whether labelling women as having below-normal BMD has adverse effects. Compared with women with normal results, those with below-normal BMD values were much more likely to take measures to prevent fractures, to start hormone therapy and to take precautions to avoid falling. All this can be considered beneficial for health. Unfortunately, because the fear of falling was more prevalent amongst those with low BMD values, they also limited their activities to avoid falling.

We wonder whether it is justified to screen and then possibly treat asymptomatic individuals with potentially 'increased fracture risk' whilst knowing that the treatment is likely to be futile as the probability of not sustaining a fracture is many times greater than the probability of sustaining a fracture.

Overmedicalized fracture prevention

What might be a more logical or appropriate use of currently available screening options or therapeutic agents for prevention of fractures? The conclusion of a classic paper published almost 25 years ago entitled 'Strategies for prevention of osteoporosis and hip fractures' [102] is still pertinent. The

message can be succinctly summarized as follows: despite the burden of illness related to hip fractures, the main ways to prevent these fractures have not changed in nearly 25 years: stop smoking, be active and eat well. This advice is appropriate for anyone whether or not they are worried about osteoporosis and has advantages for the entire human body, including the brain, heart, skin and bones.

The prevailing pharmacological fracture prevention strategy is conceptually appealing because it is relatively simple. However, key facts about hip fracture patients should be noted: they are generally old (mean age around 80 years) and undeniably frail. Regrettably, bone-targeted pharmacotherapy has, at best, minimal effect on the incidence of fractures and on fracture-related mortality [45] and is associated with adverse effects. Unnecessary labelling of asymptomatic individuals also has adverse consequences, and the strategy squanders limited healthcare resources.

Given all this, should 'osteoporosis' be added to a long list of diagnoses [103, 104] for which doing less, or even nothing, is better than our contemporary practice?

Conflict of interest statement

PA reports other interests (owning shares) with regard to Addbio AB, grants and nonfinancial support from Eli Lilly Corp and nonfinancial support from Amgen, not related to the submitted work. All other authors have nothing to disclose.

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Correspondence: Teppo L. N. Järvinen, MD, PhD, Clinical Medicine/Department of Orthopaedics and Traumatology, University of Helsinki, Tukholmankatu 8 B (6th floor), P. O. Box 20, Biomedicum, Helsinki 00014, Finland.
(fax: +358 2941 26638; e-mail: teppo.jarvinen@helsinki.fi). ■