# *Low-trauma fractures without osteoporosis*

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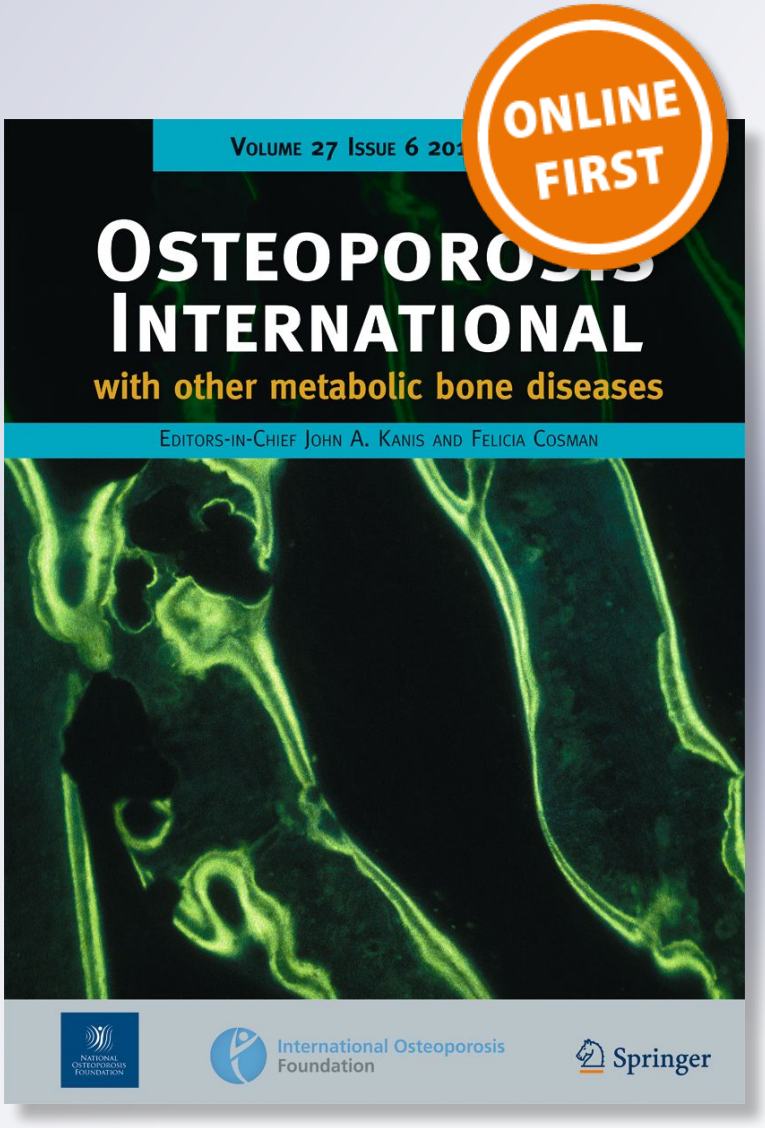


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REVIEW

# Low-trauma fractures without osteoporosis

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**Abstract** In clinical practice, areal bone mineral density (aBMD) is usually measured using dual-energy X-ray absorptiometry (DXA) to assess bone status in patients with or without osteoporotic fracture. As BMD has a Gaussian distribution, it is difficult to define a cutoff for osteoporosis diagnosis. Based on epidemiological considerations, WHO defined a DXA-based osteoporosis diagnosis with a T-score <−2.5. However, the majority of individuals who have low-trauma fractures do not have osteoporosis with DXA (i.e., T-score < −2.5), and some of them have no decreased BMD at all. Some medical conditions (spondyloarthropathies, chronic kidney disease and mineral bone disorder, diabetes, obesity) or drugs (glucocorticoids, aromatase inhibitors) are more prone to cause fractures with subnormal BMD. In the situation of fragility fractures with subnormal or normal BMD, clinicians face a difficulty as almost all the pharmacologic treatments have proved their efficacy in patients with low BMD. However, some data are available in post hoc analyses in patients with T score >−2. Overall, in patients with a previous fragility fracture (especially vertebra or hip), treatments appear to be effective. Thus, the authors recommend treating some patients with a major fragility fracture even if areal BMD T score is above −2.5.

**Keywords** BMD · Diagnosis of osteoporosis · Low-trauma fracture · Normal BMD · Treatment of osteoporosis

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## Introduction

The number of fractures is increasing worldwide because of the increase in the number of frail elderly people at high risk of falls and fractures. Low trauma fractures have individual and societal consequences in morbidity, healthcare costs, and mortality. Recognizing the conditions that increase the risk of such fractures is thus required in order to prevent part of their burden. The strength of bone is related to its mass, which can be easily estimated by areal bone mineral density (aBMD) measurements. Experimental data showed that aBMD is a good proxy of actual bone strength (actually better at the femur, than at the spine). Thus, the World Health Organization (WHO) defined osteoporosis based on aBMD by using T-scores, i.e., the number of standard deviations below the mean aBMD for young adults, T <−2.5, is the widely used definition of osteoporosis [1].

However, a proportion of fractures occur in subjects with T-scores which do not reach the osteoporotic threshold. Half of the hip fractures are observed in subjects with a T-score higher than −2.5 and 6% with a T-score higher than −1, i.e., "normal" [2]. The healthcare burden represented by non-trauma

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fractures, including hip fractures, in women with a T-score >−2.5 may thus be large. This raises a number of questions: How can we define a normal aBMD? Are the fractures the same in patients with/without densitometric-based osteoporosis? How can we manage these patients?

## What is a normal BMD?

A normal aBMD is defined by T-score >−1 [1]. This is necessarily arbitrary, as the relationship between decreased aBMD and increased risk of fracture is continuous, without a cutoff value between "at risk" and "no risk" people. BMD has a Gaussian distribution, whatever the age, not a bimodal one, and thus it is not possible to define a subgroup of individuals with a very low value. The threshold of −2.5 to define osteoporosis was chosen to produce a prevalence of femoral neck osteoporosis in white women aged 50 years and more similar to the estimated lifetime risk of hip fracture in this population (15%). In contrast, there is no biological or clinical rationale for the threshold of −1. The term "osteopenia," i.e., T-score between −1 and −2.5, was intended to allow comparisons among studies and to improve the description of characteristics of populations, not to suggest a medical intervention. The risk of fracture may be dramatically higher for a T-score of −2.3 than for a T-score of −1.2, although these values are both in the osteopenic range. Moreover, as this definition is broad, the majority of individuals are osteopenic, which disqualifies the term to define a disease. But the number of fractures is higher in this large number of people at lower risk than in the small number of people at high risk (according to aBMD level) [3, 4]. By using such definitions, the proportion of individuals aged 55–85 years with normal aBMD is 20–30%, and 13 and 18% of all non-vertebral fractures in women and men, respectively, occur in those with normal aBMD [5]. In a population of women aged 51 ± 3 years, the 10-year risk of hip, spine, shoulder, or vertebral fracture varies from 10.7 to 6.3% for those having a T-score from −1 to +1 at baseline, respectively [6]. In women aged 65 years and older, the proportion of fractures attributable to a T-score <−2.5 is low, ranging from 10 to 44% [7]. Vertebral fractures are the hallmark of osteoporosis, and they have a higher predictive value of incident fractures than low aBMD. Interestingly, anti-osteoporotic treatments have greater effect in the primary or secondary prevention of vertebral fractures, than of other fractures. The severity and number of vertebral fractures are related to deteriorated bone microarchitecture [8], and they can occur without aBMD-related osteoporosis.

The reasons for aBMD to evaluate only part of bone strength are well-known. There are limitations related to the technique of measurement, including artifacts related to spine osteoarthritis and degenerative intervertebral discs and pitfalls related to the two-dimensional technique, which does not measure directly the volumetric BMD. Measuring the spine and hip by dual-energy X-ray absorptiometry underestimates the role of cortical bone and cortical porosity in bone fragility. Moreover, a number of qualitative parameters are determinants of bone strength but cannot be assessed easily. Finite element analysis based on high-resolution computed tomography images can assess bone strength and is a significant stronger predictor of fracture than aBMD [9]. However, there is no cutoff to define a normal bone strength [10, 11], and thus, diagnosis of osteoporosis by this method has the same issues than BMD definition.

## Burden of non-trauma fracture in subjects with non-osteoporotic bone mineral density

Data from several cohorts offer the opportunity to examine the fracture incidence in general population, according to gender, clinical risk factors, age, and baseline BMD classified as normal (T-score >−1), intermediate (−2.5 < T-score <−1), or low (T-score <−2.5).

In 2651 peri-menopausal and early postmenopausal women (mean age 54 +/− 4 years), followed over 13.4 years, 415 women sustained a first low-energy fracture and 145 fractures occurred at the wrist, spine, humerus, or hip [12]. The women with fracture were slightly older (54.8 vs 53.4 years), and spine aBMD was lower in women with fracture (0.96 vs 1.03 g/cm$^2$). Three determinants were associated with fracture risk: previous fracture (OR 2.5), femoral or spine aBMD (OR 1.7 and 1.4), and absence of estrogen therapy (OR 2.1). However, 22.2% of these fractured women had a T-score >−1 and 50.7% of them had a T-score between −2.5 and −1. In the SOF study [13], 6252 women aged 65 and older were followed over 10 years and 1011 major fractures and 368 hip fractures were observed. In this study, 1154 women had a femoral neck T-score >−1; 6.3% of them experienced a non-traumatic fracture and 1.2% a hip fracture. Furthermore, 3791 women had a femoral neck T-score between −2.5 and −1: 15.7% of these women experienced a non-traumatic fracture and 4.7% a hip fracture. Among the 1011 major fractures, 569 (63.3%) occurred in women with femoral neck T-score >−2.5. Among the 176 hip fractures, 190 (52.7%) occurred in women with femoral neck T-score >−2.5. The Rotterdam study [5] included 7806 men and women (aged 55 and over) and examined the relationship between baseline aBMD and fracture incidence, during 6.8 years. As illustrated in Table 1, in this last study, a substantial percentage of fractures occurred in men and women without aBMD osteoporosis [5]. There was no strong relationship between femoral neck aBMD and middle forearm, middle arm, and ankle fractures. In men and women older than 75 years, 15% of patients with fracture had a normal aBMD. The Manitoba study [14] explored the relationships between aBMD and fracture incidence for each

**Table 1** Main characteristics of representative cohort studies illustrating percentages of fractured people with or without aBMD osteoporosis

| Name of the study | Type of population | Follow-up (mean ± SD) | Number of fractures | Fractured women with FN T-score >−1 (%) | Fractured women with T-score between −2.5 and −1 (%) |
|---|---|---|---|---|---|
| Menos cohort study [12] | Peri- and early postmenopausal | 13.4 ± 1.4 | 145 major fractures | 22.2% | 50.7% |
| SOF study [13] | Postmenopausal women | Over 10 years | 1011 major fractures | 7.0% | 56.2% |
| Rotterdarm study [5] | Men and women | 6.8 | 939 non-vertebral fractures | 17.9% (men) and 12.6% (women) | 61.4% (men) and 43.3% (women) |

anatomical bone site. This retrospective study used health databases and included 39,991 women aged 45 years and older. Women who experienced hip fracture had the lowest femoral T-scores. After adjustment for age, logistic regression showed that hip, pelvis, spine, and humerus fractures (i.e., major fractures) were strongly associated with decreased aBMD. The association between femoral aBMD and patella, rib, forearm, carpal, leg, and tarsal and metatarsal fractures were significant but weaker. The fractures of clavicle, metacarpal, phalanges, and ankle were not associated with femoral aBMD.

## Which patients and which diseases are concerned with fragility fractures and normal aBMD?

In the following section, we described some diseases and drugs which induce bone fragility and increase fracture risk that cannot be fully explained by decreased aBMD.

### Drug-induced bone fragility

Glucocorticoid (GC)-induced osteoporosis is the paradigm of the mismatch between aBMD and fracture risk. Among patients with corticosteroid-treated asthma and vertebral fracture, 11 of 32 have an aBMD at or above fracture value obtained from controls with postmenopausal osteoporosis [15]. Using data obtained from two randomized studies for prevention and treatment of GC-induced osteoporosis, Van Staa et al. underlined that at any given level of femoral neck or lumbar spine aBMD, fracture incidence is higher in users versus non-users of GCs [16]. Furthermore, in a meta-analysis of the epidemiology of GC-induced osteoporosis, the fracture risk is not closely associated with observed aBMD [17], and despite a decrease of only 0.79 SD in lumbar spine aBMD, there is in GCs users a sixfold increase in the risk of vertebral fracture compared with non-users [18]. The mechanisms behind the striking increase in fracture risk observed with GC treatment might be associated with alterations in both bone microarchitecture [19] and material bone properties [20] imperfectly captured by aBMD.

The resulting estrogen depletion associated with the use of aromatase inhibitors (AIs) is characterized by adverse effects on aBMD and on fracture risk [21, 22]. It has been previously suggested that during usual duration of adjuvant endocrine therapy, none of the women with a T-score >−1.5 at the beginning of the treatment with AI neither became osteoporotic (T-score ≤−2.5) nor experienced fracture over 5 years [23]. However, the recent results of the ABCSG-18 study challenges this statement [24]. More than 10% of the women receiving an AI with a normal aBMD (T-score ≥−1) at baseline experienced a clinical fracture during the study period [24]. It is possible that detrimental effects of AIs on bone might be imperfectly captured by conventional dual-energy X-ray absorptiometry

(DXA), as they are mainly related to a huge increase in bone resorption related to profound estrogen deficiency. It has been observed that microarchitectural damage (as measured using HRpQCT) associated with the use of exemestane was imperfectly reflected by changes in aBMD [25].

### Secondary osteoporosis, "normal" aBMD, and fractures

Inflammation-induced bone loss is one of the extra-articular manifestations associated with spondyloarthropathies [26]. Reduction in aBMD has been detected in patients with ankylosing spondylitis (AS), including AS patients, exhibiting bone formation as reflected by new syndesmophytes [27, 28]. The risk of clinical vertebral fracture is increased in patients with AS [29]. In a large survey including 390 men and women with spondyloarthropathy, 11.8% had a vertebral fracture mostly at the thoracic spine [30]. In this study, the majority of patients had a T-score >−1; in addition, the mean T-scores of the subgroup of patients with vertebral fracture were respectively 0.13, −1, and −0.59 at the lumbar spine, femoral neck, and total hip, respectively [30]. This data implies that biomechanical performance of vertebrae in SpA is not correctly assessed by DXA.

aBMD measured by DXA might be misleading in patients with chronic kidney disease (CKD) and mineral bone disorder [31, 32]. aBMD does not allow to discriminate the specific mineral bone disorder associated with the type of renal osteodystrophy [33]. For a given aBMD, four situations might be encountered: osteoporosis characterized by low bone mass with normal mineralization, secondary hyperparathyroidism characterized by normal or high bone mass with decreased mineralization, osteomalacia characterized by normal bone mass but impaired mineralization, and adynamic bone disease characterized by low bone mass, low bone turnover, and increased mineralization. In patients with mixed lesions, aBMD at the spine was found to be 2.85 SD higher than normal, compared with −0.77SD which is lower in the case of severe osteitis fibrosa [34]. Nevertheless, about one out of two patients on chronic hemodialysis will sustain a fracture [35, 36]. aBMD has been inconstantly associated with fracture in dialysis patients [37], although the updated review and meta-analysis of the link between fractures in predialysis and dialysis CKD with aBMD concluded that a low aBMD can discriminate fracture status in stage 3–5 CKD [38]. In this population, a low aBMD is associated with an increased fracture risk, but numerous fractures occur at normal aBMD [38].

A direct deleterious effect of diabetes on the cortical bone and on other qualitative parameters that are determinants of bone strength might account for the accentuated bone weakness in diabetic patients with normal or increased aBMD [39, 40]. Patients with type 2 diabetes (T2D) can have fractures with an aBMD T-score >−1.5 [41, 42]. In addition, the increased risk of vertebral fracture in T2D patients is independent of diabetic complications [41] and confirmed in well-controlled TD2 patients as reflected by glycosylated hemoglobin (Hb A1c) (45). In a cross-sectional study of female patients with T2D compared with postmenopausal women [43], lumbar spine aBMD values were higher in T2D women. Consistent with the concept that in older adults with T2D there is an increased fracture risk at a given aBMD, it was shown that a T-score in diabetic women was associated with hip fracture risk identical to control women without diabetes but with a given T-score about 0.5 units lower [44]. Contributing to a higher risk of fracture in both types of diabetes, more frequent falls have been evidenced in prospective studies [45]. However, after adjustment for history of falls, there was still an association between diabetes and fracture risk [46]. Due to their preserved aBMD, in patients with type 2 diabetes, a risk prediction model such as the FRAX algorithm might contribute to a better prediction of fracture risk. However, it has been shown in retrospective studies that the FRAX tool underestimated fracture risk in patients with diabetes [44, 47] and thus concerns still remain for using it [48].

The worldwide prevalence of obesity and particularly in western societies has increased dramatically [49]. For a long time and until recently, it was considered that obesity was a protective factor against osteoporosis and fractures [50]. However, the detrimental effects of obesity on bone health are more and more studied and recognized [51–55]. The initial finding suggesting that obesity and osteoporotic fractures were not antithetic was provided by the data from the fracture liaison service (FLS) of Cambridge [56]. In this database, there was an unexpectedly high prevalence of obesity in patients attending the FLS; in addition, 80.4% of obese and 89.4% of morbidly obese patients had a T-score higher than −1 [56]. These findings were confirmed by the investigation of the prevalence of clinical fractures in obese postmenopausal women enrolled in the Global Longitudinal study of Osteoporosis in Women (GLOW) [57]. Furthermore, in the obese women with incident non-vertebral fracture subgroup enrolled in the Study of Osteoporotic Fractures, the mean T-scores at the total hip and lumbar spine were −1.12 and −1.26, respectively [58]. Even in this population, aBMD assessment may still give relevant information concerning bone fragility; a decrease in femoral neck BMD was independently associated with incident non-vertebral fracture [58]. Despite having almost normal aBMD, obese women with the lowest aBMD had the highest risk of fracture [59]. Obese women with fracture might have unadapted aBMD and bone strength not commensurate to their high body mass index [60].

## Fragility fractures with normal mineral density: which management?

Most of the studies assessing the pharmacological treatments have included patients with low aBMD. There is no clinical

study dedicated to patients with fractures and normal BMD. For some studies, post hoc analyses assessed the effect of treatment in defined subgroups of individuals with T-scores above the threshold for osteoporosis; pitfalls of these post hoc analyses are well-known and preclude any definite conclusion. Some studies analyzed baseline characteristics, such as age and T-scores, as determinants of treatment effect, looking at interactions. Finally, some studies were conducted without T-score definitions, allowing analysis in subjects defined primarily by non-trauma fractures.

Non-pharmacological management of bone fragility is identical in these circumstances that it is for patients with low aBMD as it is for both calcium and vitamin D supplementation, prevention of falls, and use of tools to prevent consequences of falls. This later point should be emphasized since in the absence of low aBMD, falls should be considered as a major factor in the occurrence of non-vertebral fractures.

## Bisphosphonates

### *Alendronate*

In the FIT 1 study [61], inclusion criteria were presence of at least one vertebral fracture at baseline and a T-score at the hip <−2 (manufacturer data). However, after publication of the standards NHANES III, a "real" inclusion T-score was higher (<−1.6). This study is especially instructive with respect to the purpose of this review since the patients included had an aBMD finally on average for their age, although analyses focused on women with T-score >−1 are not available. Under these conditions, ALN has proven its efficacy with a significant reduction in the risk of vertebral fracture compared to placebo: relative risk 0·53 (95% CI 0.41–0.68). The risk of any clinical fracture, the main secondary endpoint, was lower in the alendronate than in the placebo group: relative hazard 0.72 (95% CI 0.58–0.90). The relative hazards for hip fracture and wrist fracture for ALN versus placebo were 0·49 (95% CI 0.23–0.99) and 0.52 (95% CI 0.31–0.87), respectively.

### *Risedronate*

A study was conducted from the two pivotal studies VERT MN and VERT NA [62]. Inclusion criterion for the study VERT MN was by the presence of at least two FVs. For the VERT NA study, criteria were T-score <−2 at the lumbar spine and at least 1 vertebral fracture. For women with at least two vertebral fractures, there was no aBMD threshold. From these two studies, Kanis et al. [62] have focused only on patients included on the basis of prevalent vertebral fracture corresponding to 892 in the placebo group and 910 in the RIS group. Overall, after 3 years of treatment, there was a reduction in the risk of vertebral fracture for women treated by RIS compared to placebo by 44% (95% CI 28–56%). The authors then conducted analyses to determine the impact of aBMD at baseline on the treatment effect. Overall, there was no difference in efficacy based on this parameter. The authors especially compared patients whose T-score was below or above −2.5 (lowest site at baseline). In the 1st and after multiple adjustments, the OR was 0.55 (95% CI 0.41–0.74) and in seconds 0.41 (95% CI 0.24–0.69). By taking into consideration the baseline T-score at the lumbar spine or femoral neck instead of the lowest site, the results were similar. Similarly, the effectiveness of the treatment was identical according to the number of prevalent vertebral fractures regardless of the level of aBMD at baseline and whatever the measurement site considered. However, as indicated for ALN, there is no data available for the subgroup of women with T-score >−1 at baseline.

### *Zoledronic acid*

The HORIZON 2 study assessed the efficacy of ZOL in women and men after a hip fracture [63]. Low BMD was not a criterion for inclusion in the study, and BMD T-score >−1.5 at baseline was encountered for 11.4% of the patients included. Under these conditions, the authors demonstrated an effective treatment effect for preventing the occurrence of fractures with clinical expression: OR 0.65 (95% CI 0.50–0.84). A positive effect was also observed for non-vertebral fractures OR 0.73 (95% CI 0.55–0.98), hip fractures (albeit non-significant) OR 0.70 (95% CI 0.41–1.19), and clinical vertebral fractures OR 0.54 (95% CI 0.32–0.92). The results of HORIZON 1 (HORIZON-PFT) were analyzed in order to assess the influence of baseline data (and particularly aBMD data) on the treatment efficacy. No data was available in the subgroup of patients with T-score >−1. However, the authors studied the efficacy of ZOL in patients with baseline vertebral fracture but no baseline osteoporosis (T-score >−2.5). In this population, the incidence of vertebral fracture was 4.7% in the treated group versus 13.8% in the placebo group. The results were not different in women with both a prevalent vertebral fracture and osteoporosis (T-score ≤−2.5): the vertebral fracture rate in the treated group was 3.9 versus 13.7% in the placebo group suggesting that a low influence of baseline aBMD for women with vertebral fracture at baseline regarding the efficacy of ZOL is moderate.

### *Denosumab*

Based on data from the FREEDOM pivotal study, McClung et al. studied the influence of baseline parameters on the effectiveness of treatment [64]. For women with baseline femoral T-score >−2.5 (no data is available for women with T-score at baseline >−1), the OR for vertebral fracture compared to placebo was 0.34 (95% CI 0.24–0.47); it was 0.31 (95% CI 0.21–0.47) for those with a femoral T-score at baseline ≤−2.5. Effectiveness was comparable in patients with or without baseline vertebral fracture (ORs 0.34 (95% CI 0.24–0.48) and 0.31

(95% CI 0.22–0.44), respectively). Results were similar in the presence or absence of a previous non-vertebral fracture with respective ORs of 0.38 (95% CI 0.26–0.54) and 0.29 (95% CI 0.21–0.40). However, there was no evidence of efficacy of denosumab on non-vertebral fracture prevention in patients with baseline femoral T-score >−2.5. In this study, there is no specific data for patients with a prevalent fracture (both vertebral and non-vertebral) and normal BMD.

*Teriparatide*

Inclusion criteria for entry in the pivotal study of TPT were based primarily on the presence of vertebral fractures [65]. At least one grade II or two grade I vertebral fractures were requested. In the presence of a single grade II vertebral fracture, the T-score was mandatory, but the threshold was −1 regardless of the site. Despite the absence of drastic densitometric criteria for study entry, the mean T-score at baseline was low (−2.6 both in the treated group and the placebo group). The authors then studied the influence of lumbar BMD at baseline on fracture risk by dividing patients into tertiles according to their baseline aBMD. For treated patients, there was no interaction between baseline BMD and incidence of vertebral fractures. Thus, in both the higher tertile and the middle tertile, the fracture rate was 4%; it was 7% in the highest tertile. The fracture rate in the placebo group was significantly higher in patients in the lowest tertile (22%) compared to those in the middle tertile (about 12%) and those in the top tertile (8%).

## Conclusion

Non-trauma fractures can occur in subjects with an aBMD above the osteoporosis threshold, and even with a normal aBMD. This can be explained by qualitative changes of bone as demonstrated in patients receiving GCs or AIs and in diabetic patients. This is also the reminder that aBMD is only one of the risk factors of fractures.

Although BMD is a crucial determinant of fracture risk, the overall detection rate for spine, hip, forearm, and proximal humerus fracture is low, and indeed, 96% of fractures at the hip, spine, proximal humerus, or forearm will occur in women without osteoporosis [66, 67]. Fracture prediction tools like the FRAX, the Garvan fracture risk calculator, and Qfracture™ have been developed to improve the assessment of fracture risk by including clinical risk factors. Concerns still remain for using such fracture risk tools [68] as shown in patients with diabetes type II [48]. Experts from the National Bone Health Alliance Working Group support the use of the term "osteoporosis" for postmenopausal women and men over the age of 50 years who have experienced a low-trauma hip fracture and for those who have osteopenia by BMD who sustain a low-trauma vertebral, proximal humerus, pelvis, or in some cases distal forearm fracture. The entity of "clinical osteoporosis" has been also defined by the American College of Endocrinology and the American Association of Clinical Endocrinologists as the following: "Osteoporosis should be diagnosed based on presence of fragility fractures in the absence of other metabolic bone disorders or a T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius even in the absence of a prevalent fracture" [69]. Thus, many experts are considering patients with low trauma fractures (without low BMD) to be at higher risk for future fractures.

Few data are available to assess efficacy of pharmacologic treatments in individuals with low trauma fracture and normal aBMD. Treatment after a recent fragility hip or vertebral fracture is recommended worldwide, recognizing the severity of this type of fractures (according to quality of life and mortality) and the potential discrepancy between these fractures and aBMD. Indeed, hip, vertebral, pelvic, and proximal humeral fractures are associated with significant excess mortality rate [70–73] and a higher risk of subsequent fractures. We recommend to consider treatment of patients with such fracture associated with femur or lumbar spine aBMD T-score <−1, fully recognizing the paucity of the data supporting this recommendation.

Thus, the authors recommend treating some patients with a major fragility fracture even if the areal BMD T-score is above −2.5. In other situations, clinical judgment is mandatory to assess the individual risk-benefit of a treatment.

**Authors' contributions** Authors have all equally contributed to the conception, drafting of the article, and critical and final approval of the article.

**Compliance with ethical standards**

**Conflicts of interest** E.L: occasional interventions: honoraria as an expert or speaker for Amgen, Expanscience, Lilly (France), MSD. Indirect interests: financial support to a research organization from Abbvie, Amgen, Lilly (France), MSD, UCB. B.C: occasional interventions: honoraria as an expert or speaker for Amgen, Expanscience, Lilly (France), MSD Medtronic, Roche diagnostics. Indirect interests: financial support to a research organization from Amgen and MSD. E.Legrand: honoraria as an expert or speaker for Amgen. P.G: Invitation conference and congress for AMGEN, Lilly, Novartis, Pfizer, Roche. C.R: occasional interventions: honoraria as an expert or speaker for Alexion, Amgen, Lilly (France), MSD, and UCB. Funding is from ULTRAGENYX.

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