Osteopenia: is it a problem?

Osteopenia is used in bone densitometry reports when the T-score is between -1 and -2.5. It is not a disease category, but rather a situation requiring the assesment of associated risk factors for fractures. Subjects with osteopenia should not be treated but be reassured. Osteopenia is defined too broadly to be a useful fracture risk. However, follow-up densitometry must be targeted to patients with the lowest values of osteopenia. Patients with osteopenia and prevalent vertebral fractures should be considered as osteoporotic patients and treated appropriately.

KEYWORDS: bone densitometry ■ fracture risk ■ osteopenia ■ osteoporosis ■ vertebral fracture

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When osteoporosis was defined by the presence of a fracture, osteopenia was used by radiologists to described an excess of translucency of bones. Osteopenia is now used in bone densitometry reports when the T-score is between -1 and -2.5 standard deviations below the sex-matched control's peak bone mass, according to a working group of the World Health Organization (WHO) [1]. This definition has had widespread success and is used daily worldwide. However, in contrast to the relevance of the -2.5 T-score threshold for osteoporosis, there is no biological or epidemiological rationale for the threshold of -1. The initial objective was to allow a comparison among studies and to clarify scientific communication, but, as the use of the densitometric definition of osteoporosis (T < -2.5) has been largely encouraged, the densitometric definition of the so-called osteopenia is currently being incorporated into reports from densitometry devices. This induces, from both the patients and the physicians, questions regarding the relevance of osteopenia and the necessity of treatment of these subjects. So, let us consider these questions through epidemiological and therapeutic data.

Is osteopenia a disease?

The original intention of the WHO was to choose a threshold that would make osteopenia uncommon at the time of menopause. Providing that peak bone mass is constant up to the age of menopause, the expected proportion of individuals having a T-score between -1 and -2.5 would be 16% at the age of 50 years, according to the Gauss distribution of bone mineral density (BMD) values. Actually, the prevalence of osteopenia is higher, and is at least 50% in postmenopausal women over the age of 50 years [2]. Osteopenia is not a disease category, thus, we should not talk about osteopenia as a diagnosis, as learning that bone density is below normal may lead to persistent anxiety; 3 months after receiving a BMD result, it has been demonstrated that women who have high levels of pre-existing general health anxiety have higher rates of anxiety regarding osteoporosis [3]. Subjects with osteopenia should be reassured. Osteopenia is rather a situation for counseling patients regarding changing risk factors and lifestyle.

Is osteopenia a predisease?

Prehypertension or impaired fasting glucose have been defined for selecting patients at increased risk of hypertension or diabetes. Is osteopenia a means to capture individuals who will develop osteoporosis in the next years? BMD decreases after the menopause, and the rate of bone loss varies among individuals. In a large prospective study, a cohort of healthy postmenopausal women was followed for 6 years [4]. At baseline, the T-score was -0.8 ± 0.9, which is a normal and expected result in this population with an average age of 53 years. Mean bone loss was -3% over 6 years. It was -2.2 ± 5.1% in 73 women with T being -2.5 or lower at baseline, and -3.0 ± 3.9% in 83 women who had -0.6 less than or equal to a T-value of less than or equal to -1.4 at baseline. Thus, the occurrence of osteoporosis – that is, the probability to fall below the threshold of a T-score of -2.5 – is very unexpected in subjects with

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osteopenia, at least in those with the highest values of T-scores. Therefore, there is no indication that osteopenia detects patients who will have osteoporosis over the next years. Follow-up densitometry must be targeted based on baseline BMD – only individuals in the lowest part of the osteopenia category should have short-term BMD measurements repeated [5].

Is osteopenia a risk factor for fractures?

A growing number of reports show that many women who fracture have a BMD higher than that associated with osteoporosis. In the Study of Osteoporotic Fractures (SOF), conducted prospectively in women aged 65 years and older, half of the 243 women with incident hip fractures were not osteoporotic at baseline. Even at the femoral neck itself, BMD measurement did not detect osteoporosis in 37% of hip fracture cases [6]. In the NORA study, the fracture rate increased with age and low BMD, but there were so many more women with osteopenia than with osteoporosis that the number of fractures observed during follow-up was actually greater among subjects with osteopenia than among patients with osteoporosis [7]. In women older than 60 years who have clinical risk factors for osteoporosis, but only osteopenia by BMD measurements, systematic spine x-rays identified vertebral fractures in 21% of subjects [8]. Indeed, this information was known for one patient in four, but no action had been taken. Considering the patients presenting with a nonvertebral fracture, 20% of them have vertebral fractures, and approximately half have multiple fractures [9].

These data show that fractures can be observed in patients with osteopenia (as well as in patients with normal BMD). The problem is that osteopenia is defined too broadly to be a useful index of fracture risk, and one can speculate that the fracture risk is not similar for a T-score of -1.1 and a T-score of -2.4. BMD is only one of the many factors that independently influence fracture risk.

Age is a strong risk factor and increases fracture risk regardless of BMD. Osteopenic women in their 50s have a very low risk of fracture. A woman aged 55 years with a T-score of -2 has a 5-year risk lower than 5% for suffering a vertebral fracture, and approximately a 0% risk of suffering a hip fracture [10].

Vertebral fracture is the other cornerstone for the estimation of fracture risk, independent of BMD [11]. Even in osteopenic patients, there is a dose effect of this risk factor – the higher the number of fractures and the more severe they are, the higher the risk is of future fractures. Across the range of osteopenia, prevalent vertebral fractures have a strong impact on the risk of incident fractures. In such patients, BMD alone underestimates the actual risk of fracture.

Finally, at any given BMD, the risk of fracture depends on concomittant factors such as falls [12]. In the OFELY study, involving 671 women aged 62 years, 322 women had osteopenia; the 10-year risk of fracture was driven by a T-score of less than -2 and/or prevalent fracture and/or increased bone alkaline phosphatase in the highest quartile [13]. The key point of this prospective study was that the survival probability without fracture was similar for osteopenic women and normal women on one hand, and on the other hand, the risk of sustaining a fracture was similar for osteoporotic and osteopenic patients. Similar data have been published in Australia, showing prospectively that the burden of incident fractures is similar in patients with osteoporosis and in patients with osteopenia and prevalent fractures [14].

So, women with modestly reduced BMD and fracture are equivalent to those with osteoporosis in terms of risk of fracture. Because of their large number, the population burden of fractures originates in women with osteopenia and risk factors including fractures, not osteoporosis.

An unresolved question is whether or not the prediction of fracture in osteopenic women is improved by using longitudinal changes in BMD. In the SOF study, the prediction of all types of fractures was similar for initial BMD measurement, or repeated BMD measurements [15]. In a recent Canadian study, the risk of fragility fractures in patients with osteopenia was better estimated by models that included BMD changes rather than baseline BMD only, suggesting that women who fracture with BMD levels in the range of osteopenia may be those with a high rate of bone loss [16].

Should subjects with osteopenia receive treatment?

Subjects with osteopenia should receive calcium and vitamin D to achieve the current recommended levels, in particular, for the serum 25-OH vitamin D concentration. Advice can be given concerning weight-bearing exercices, recognizing that the best type,

frequency and amount of exercise for decreasing the risk of fracture is to be adapted for each individual.

Post-hoc analyses have been conducted in large clinical trials, after selection of patients with osteopenia, to assess the potential effect of treatments.

In the Multiple Outcomes in Raloxifene Evaluation (MORE) trial, assessing the bone effect of raloxifene, 2557 patients had osteopenia at the hip, and raloxifene decreased the risk of vertebral fracture by 47%; importantly, the lumbar spine T-score of this population was low, that is, -2.3 [17]. The site of definition of osteopenia is highly relevant, as there was no antifracture effect when patients were defined as osteopenic using the lumbar spine T-score only. Moreover, the incidence of fractures in the placebo group was 3.5% over 3 years. So, although the relative risk reduction was high and significant, the absolute risk reduction was low – less than 1%. The same conclusions can be drawn from data obtained with strontium ranelate: in women with osteopenia, the relative risk of vertebral fractures was decreased by 59% in the treated patients, but the absolute risk reduction was in the order of 5% [18]. Therefore, we have evidence of the effectiveness of these drugs in this population of patients with osteopenia, but the benefit appears very low.

A decrease in the risk of fracture in osteopenic patients has also been demonstrated for risedronate [19]. These patients had a T-score of -1.8 at the femoral neck and there was a significant decrease of both vertebral and nonvertebral fractures, a category of fractures on which no data are provided in other studies. However, when osteopenia was defined as having a T-score between -1 and -2.5 at both the femoral neck and lumbar spine – that is, a 'true' osteopenia at both sites – there was still a trend, but a loss of the significance of the result. Alendronate does not reduce the risk of nonvertebral fracture in osteopenic women [20], and has a small benefit on the risk of vertebral fractures in a population of postmenopasual women with a mean T-score of -2.1 and a very low incidence of fractures. This study was recently reanalyzed in order to discover whether a history of nonvertebral fracture in patients without osteoporosis could identify patients for whom alendronate reduces the risk of nonvertebral fracture incidence; there was no observed effect of the treatment in this selected population [21,22].

Taken together, these data suggest that management of patients based on T-scores may be difficult, as the risk of fracture is very different in patients with a T-score of -1.5 and a T-score of -2.4, but probably not so different between those with T-scores of -2.4 and -2.6. Decision making regarding treatments in postmenopausal women should not be based on T-scores alone, for which there is a growing dissatisfaction, but instead on an estimation of the patient's risk of fracture. FRAX® is a meaningful tool for that [23]. Studies are ongoing to assess the efficacy of therapeutic interventions as a function of an absolute fracture risk, and will challenge the historical question of indication and efficacy of a drug based on BMD categorization.

Owing to the large number of patients with osteopenia, cost–effectiveness must be considered as far as a treatment is discussed. A cost-effective use of the healthcare resources is the function of both the baseline risk and the effect of intervention. Thus, treatments are certainly not cost effective in patients with osteopenia, as we have shown that the benefit is very low [24]. But, as shown previously, patients with osteopenia should be considered for treatment if they have other risk factors, including fractures. Therefore, the question is not the cost–effectiveness of a treatment in women categorized by T-score, but rather the cost–effectiveness of a strategy, including selection of high-risk patients (i.e., diagnosis of vertebral fractures) and treatment of selected patients. Recent data suggest that this strategy is cost effective, with a benchmark in use of

Executive summary

- Osteopenia is not a disease category.
- Subjects with osteopenia should not receive treatment.
- Osteopenia is a situation to reassure the patients and to counsel them regarding changing risk factors and lifestyle.
- Concomittant risk factors for fractures must be checked carefully in patients in the lowest part of the osteopenic range.
- Fracture risk is similar in patients with osteopenia and prevalent vertebral fractures, and in patients with osteoporosis.

US$50,000/quality-adjusted life year, so the cost would be between US$18,000 for a 60-year-old woman with T-score of -2.4 and US$77,000 for an 80-year-old women with a T-score of -1.5 [25,26]. Such estimates can also be made, with similar results, with other underlying risk factors, such as maternal history of hip fracture.

Conclusion

Osteopenia is not a disease, and the word should not appear on densitometry report. Patients with such results should receive information that they are not suffering from osteoporosis and that they should not be treated. However, underlying risk factors must be checked appropriately, especially in patients with a T-score of -2 or less. Moreover, patients with osteopenia and prevalent vertebral fractures should be treated as osteoporotic patients.

Future perspective

There is a growing dissatisfaction with the T-score categories. In the future, biochemical assessments of bone turnover and noninvasive microarchitecture assessment tools will help to select patients who should receive the highest priority for prevention and treatment.

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Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 World Health Organization: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO Study Group. *World Health Organ. Tech. Rep. Ser.* 843, 1–129 (1994).

2 Kanis JA, Mc Closkey EV, Johansson H, Oden A, Melton LJ III, Khaltaev N: A reference standard for the description of osteoporosis. *Bone* 42, 467–475 (2008).

3 Rimes KA, Salkovskis PM: Prediction of psychological reactions to bone density screening for osteoporosis using a cognitive-behavioral model of health anxiety. *Behav. Res. Ther.* 40, 359–381 (2002).

4 McClung MR, Wasnich RD, Hosking DJ *et al.*; on behalf of the Early Postmenopausal Intervention Cohort (EPIC): Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort study. *J. Clin. Endocrinol. Metab.* 89, 4879–4885 (2004).

5 Abrahamsen B, Vestergaard P, Rud B *et al.*: Ten-year absolute risk of osteoporotic fractures according to BMD T score at menopause: the Danish Osteoporosis Prevention Study. *J. Bone Miner. Res.* 21, 796–800 (2006).

6 Wainwright SA, Marshall LM, Ensrud KE *et al.*; for the Study of Osteoporotic Fractures research group: Hip fracture in women with osteoporosis. *J. Clin. Endocrinol. Metab.* 90, 2787–2793 (2005).

7 Siris, ES, Miller PD, Barrett-Connor E *et al.*: Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women. Results form the National Osteoporosis Risk Assessment. *JAMA* 286, 2815–2822 (2001).

▪▪ **First study to demonstrate the burden of fractures in an osteopenic population.**

8 Netelenbos JC, Lems WF, Geusens PP *et al.*: Spine radiographs to improve the identification of women at high risk for fractures. *Osteoporos. Int.* 20(8), 1347–1352 (2009).

9 Miller PD, Barlas S, Brenneman SK *et al.*: An approach to identifying osteopenic women at increased short-term risk of fracture. *Arch. Intern. Med.* 164, 1113–1120 (2004).

10 Cummings SR, Bates D, Black DM: Clinical use of bone densitometry: scientific review. *JAMA* 288, 1889–1897 (2002).

11 Siris ES, Genant HK, Laster AJ, Chen P, Misurski DA, Krege JH: Enhanced prediction of fracture risk combining vertebral fracture status and BMD. *Osteoporos. Int.* 18, 761–770 (2007).

12 Nguyen ND, Pongchaiyakul C, Center JR, Eisman JA, Nguyen TV: Identification of high-risk individuals for hip fracture: a 14-year prospective study. *J. Bone Miner. Res.* 20, 1921–1928 (2005).

13 Sornay-Rendu E, Munoz F, Garnero P, Duboeuf F, Delmas PD: Identification of osteopenic women at high risk of fracture: the OFELY study. *J. Bone Miner. Res.* 20, 1813–1819 (2005).

14 Pasco JA, Seeman E, Henry MJ, Merriman EN, Nicholson GC, Kotowicz MA: The population burden of fractures originates in women with osteopenia, not osteoporosis. *Osteoporos. Int.* 17, 1404–1409 (2006).

15 Hillier TA, Stone KL, Bauer DC *et al.*: Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women. *Arch. Intern. Med.* 167, 155–160 (2007).

16 Berger C, Langsetmo L, Joseph L *et al.*; The CaMos Research Group: Association between change in BMD and fragility fracture in women and men. *J. Bone Miner. Res.* 24, 361–370 (2009).

17 Kanis JA, Johnell O, Black DM *et al.*: Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: a reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial. *Bone* 33, 293–300 (2003).

18 Seeman E, Devogelaer JP, Lorec R *et al.*: Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. *J. Bone Miner. Res.* 23, 433–438 (2008).

19 Siris ES, Simon JA, Barton IP, McClung MR, Grauer A: Effects of risedronate on fracture risk in postmenopausal women with osteopenia. *Osteoporos. Int.* 19, 681–686 (2008).

20 Cummings SR, Black DM, Thompson DE *et al.*; for the Fracture Intervention Trial Reserarch Group: Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. *JAMA* 280, 2077–2082 (1998).

21 Ryder KM, Cummings SR, Palermo L *et al.*; for the Fracture Intervention Trial Research Group: Does a history of non-vertebral fracture identify women without osteoporosis for treatment? *J. Gen. Intern. Med.* 23(8), 1177–1181 (2008).

22 Quandt SA, Thilpson DE, Schneider DL, Nevitt MC, Black DM, for the Fracture Intervention Trial Research Group: Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of -1.6 to -2.5 at the femoral neck: the fracture intervention trial. *Mayo Clin. Proc.* 80, 343–349 (2005).

23 Roux C, Thomas T: Optimal use of FRAX. *Joint Bone Spine* 76(1), 1–3 (2009).

24 Schousboe JT, Nyman JA, Kane RL, Ensrud KE: Cost–effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann. Intern. Med.* 142, 734–741 (2005).

25 Schousboe JT, Ensrud KE, Nyman JA, Kane RL, Melton J: Potential cost-effective use of spine radiographs to detect vertebral deformity and select osteopenic postmenopausal women for animo-bisphosphonate therapy. *Osteoporos. Int.* 16, 1883–1893 (2005).

- **Assesses the impact of a strategy to select patients who should receive the highest priority for treatment.**

26 Schousboe JT, Ensrud KE, Nyman JA, Kane RL, Melton LJ 3rd: Cost–effectiveness of vertebral fracture assessment to detect prevalent vertebral deformity and select postmenopausal women with a femoral neck T score > -2.5 for alendronate therapy: a modelling study. *J. Clin. Densitom.* 9, 133–143 (2006).