EDITORIAL

# A Not-So-New Treatment for Old Bones

Clifford J. Rosen, M.D.

Low bone mineral density (i.e., a T score below –2.5) is the current operational definition of osteoporosis. However, low bone mineral density is actually a risk factor for fracture, not a disease marker. Notwithstanding, nearly all osteoporosis treatment algorithms are based on bone mineral density, frequently combined with the clinical risk factors of age and prevalent fractures. Given the high prevalence of low bone mineral density with advanced age, a review of the history underlying determination of risk and the concept of osteopenia is worthwhile.

When measurement of bone density was first introduced 25 years ago, absolute bone mineral density (g per square centimeter) was considered as too onerous for clinicians to understand. At that time, several population studies had shown that bone mineral density was a complex trait with a Gaussian distribution. Hence, a measurement of bone mineral density could easily be represented by the number of standard deviations by which the bone mineral density of an individual patient differed from the mean, termed a T score. Given that approximately 68% of the population should have a bone mineral density within 1 standard deviation from the mean, persons whose measurement fell at or below 2.5 standard deviations from the mean (2.5% of the population) were considered to be at highest risk for fractures.[1] Thus, clinicians tended to recommend treatment to women who had a T score below –2.5. However, it was clear that there was an intermediate, yet substantial, group of patients with a T score between –1 and –2.5 who were subsequently described as having osteopenia and were at risk for fractures, based statistically on the continuous nature of the bone mineral density distribution. The National Osteoporosis Risk Assessment study, a longitudinal examination involving more than 150,000 postmenopausal women, confirmed that the vast majority of fractures occurred in women with osteopenia.[2] Similar findings were also noted in a study involving more than 14,000 women from the Netherlands, known as the Rotterdam study.[3] Still, it was disappointing that in the Fracture Intervention Trial, a study that examined the effect of alendronate treatment on new fractures in 4432 women, treatment with alendronate did not reduce the risk of fractures among women who had bone mineral density in the osteopenic range.[4] Those data, coupled with a growing recognition of atypical femoral fractures as a very rare but devastating side effect of antiresorptive therapy, particularly among women with osteopenia, led to a rapid decrease in new prescriptions for osteoporosis, as well as less adherence to treatment among previously treated women.[5,6] Ultimately, these events led to a treatment gap in patients who had strong clinical risk factors for an osteoporotic fracture (particularly age) but had T scores in the osteopenic range.

Reid et al.[7] now report in the *Journal* the results of a 6-year, randomized, double-blind, placebo-controlled trial of zoledronate at a dose of 5 mg, administered intravenously at 18-month intervals, in 2000 postmenopausal women 65 years of age or older who had osteopenia. Three elements of this trial are unique as compared with earlier studies that showed that annual administration of zoledronate reduced the risk of fractures in older postmenopausal women.[8,9] First, the current trial showed, with sufficient statistical power, that zoledronate administered less frequently than once a year was associated with not only a greater in-



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crease in bone mass than that observed in the placebo group but also a significantly lower risk of vertebral and nonvertebral fractures. The duration of the current trial was twice that of registration trials of newer therapies.[4,8,9] Second, in contrast to the Fracture Intervention Trial of oral alendronate in women who did not have prevalent fractures but had osteopenia, treatment with intravenous zoledronate was effective in preventing fractures among women with an average T score of –1.27 at the total hip and –1.64 at the femoral neck. The reasons for this difference are not clear, although zoledronate is a more potent antiresorptive agent than alendronate, and at least one third of the participants in the current trial had clinical risk factors that placed them at higher risk for fracture (i.e., a baseline 10-year risk of hip fracture of more than 3% or a baseline 10-year risk of any osteoporotic fracture of more than 20%), even though the bone mineral density was considered to indicate osteopenia. Also, the average age of the participants in the current trial was approximately 3.5 years older than that in the Fracture Intervention Trial. Owing to the interaction between age and bone mineral density, the results of the current trial should not be extrapolated to younger postmenopausal women (50 to 64 years of age) with osteopenia. Third, 6 years of intermittent treatment with zoledronate resulted in relatively few adverse events, although the current trial was not powered to assess more rare side effects, such as osteonecrosis of the jaw and atypical femoral fractures.

Taken together, the results of the trial by Reid et al. should have an effect on clinical practice. Given the effectiveness of infrequent administration of zoledronate in reducing the risk of fragility fracture, this treatment can certainly be added to our armamentarium for treating osteoporosis, and it would represent an approach that would not be hindered by adherence issues. But just as importantly, this trial reminds us that risk assessment and treatment decisions go well beyond bone mineral density and should focus particularly on age and a history of previous fractures.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Maine Medical Center Research Institute, Scarborough.

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