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Editorial

Does low bone mineral density predict mortality?



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Major osteoporotic fractures are associated with a higher than expected age-adjusted mortality rate [1]. They are therefore considered in French recommendations for the management of postmenopausal fractures as an indication of osteoporosis drug therapy [2]. The association between major osteoporotic fractures and mortality has been found consistently in several studies.

A smaller number of investigations assessed the potential links between low bone mineral density (BMD) values and the risk of death. They are the focus of this editorial.

1. Early data (single-photon absorptiometry)

One of the earliest sources of information is the Study of Osteoporotic Fractures in a cohort of 9704 women aged 65 years or older in San Francisco [3], which served as the basis for numerous published studies. At baseline, BMD was measured at the wrist by single-photon absorptiometry. During the mean follow-up of 2.8 years, 299 women died. Each standard deviation decrease in wrist BMD was associated with a small increase in mortality (relative risk [RR]: 1.19; 95% confidence interval [95%CI]: 1.04–1.36). The measurement site associated with the best predictive value was the proximal radius. Stroke was the cause of death most closely linked to low BMD, even after adjustment for multiple factors including cardiovascular risk factors. Subsequent studies obtained similar results [4–6]. In particular, in women studied soon after the menopause, low BMD at the wrist was associated with mortality, and the association was strongest for death due to cardiovascular disease (RR: 2.3; 95% CI: 1–5.3) [4].

2. Data obtained by dual-photon X-ray absorptiometry (DXA) and other techniques for measuring bone mineral density (BMD)

Over time, the techniques used to measure BMD improved, yet the study results remained unchanged. For instance, BMD measured at the calcaneus using DXA was associated with mortality in

both men and women, even after adjustment for multiple factors. Nevertheless, as with the early studies, the association, albeit statistically significant, was of only modest strength (men: RR: 1.23; 95% CI: 1.1–1.41; women: RR: 1.19; 95% CI: 1.02–1.39).

Other techniques used to measure BMD include radiographic absorptiometry, whose relevance is controversial. In 3501 individuals, low BMD measured at the wrist using radiographic absorptiometry was associated with a 16% mortality increase (95% CI: 7–26) in men but was not associated with mortality in women [7].

3. Data obtained more recently using dual-photon X-ray absorptiometry (DXA)

For many years, DXA has been the reference standard for measuring BMD. Several studies that relied on DXA measurements produced consistent results [8–14]. For instance, in men aged 65–76 years, each standard deviation increase in BMD at the hip was associated with a 33% (95% CI: 9–34) decrease in the risk of death. An association of similar strength was found when only cardiovascular deaths were considered. Comparable findings were obtained in the NHANES cohort [9]: individuals in the lowest hip BMD quartile had a higher risk of death than those in the highest quartile (RR: 1.53; 95% CI: 1.08–2.18). In the Rotterdam cohort, BMD Z scores at the femoral neck were not associated with mortality in women; among men, in contrast, those having lower femoral neck BMD values were at higher risk for death even after adjustment for multiple factors, although the strength of the association was modest (RR: 1.14; 95% CI: 1.02–1.28) [10]. Although outside the scope of this editorial, another interesting finding is that high femoral neck BMD (Z-score > 1.5) was also associated with higher mortality.

4. Data obtained outside Europe and the US

The association linking low BMD to excess mortality has also been found outside Europe and the US. A study from Japan in 271 elderly women showed that osteoporosis defined based on the BMD value at the femoral neck was associated with an increased risk of death (RR: 2.17; 95% CI: 1.07–4.41) [11]. Mortality was also higher in individuals who were in the lowest BMD tertile or quartile. A study from Mexico published in 2016 assessed 839 elderly men and women and found that, after adjustment for multiple factors, each standard deviation decrease in total hip BMD was associated with a hazards ratio for death of 1.41 (95% CI: 1.15–1.72).

5. Bone loss and risk of death

Several studies investigated whether bone loss was associated with the risk of death [12,13]. One was conducted in the older women of the above-mentioned Study of Osteoporotic Fractures [12]. Each standard deviation increase in annual BMD loss at the hip was associated with a 1.3-fold (95% CI: 1.1–1.4) increase in mortality after adjustment for multiple factors. Similar results were obtained in an Australian cohort of women and men [13]. However, the rate of bone loss associated with mortality was high (> 5% per year) and occurred in only a minority of study participants.

6. Influence of gender

The populations included in the available studies were composed of females, males, or both. In this last case, the data were not always analyzed separately in males and females. The studies that relied on DXA to measure BMD do not seem to show any major differences between genders. In a Swedish study of elderly men, low BMD was associated with an RR for death of 1.27 (95% CI: 1.14–1.42) [14]. Some discrepancies exist, however. Thus, in the Study of Osteoporotic Fractures, which included only women, baseline hip BMD was not significantly associated with mortality [12]. In contrast, in a mixed population from Australia, baseline femoral neck BMD was associated with mortality in females but not in males.

7. Causes of death in populations with low bone mineral density (BMD)

The reasons for the association between low BMD and higher mortality are unclear. One approach used to resolve this uncertainty has involved identifying the causes of death in populations with low BMD. Special attention was given to cardiovascular deaths, as associations have been documented between cardiovascular disease and osteoporosis. A study of the NHANES III population assessed the risk of death due to coronary heart disease or stroke [15]. In men, low BMD was not associated with the risk of death due to either type of event. In females, trends were found, but there were no statistically significant associations. In contrast, in women soon after the menopause, low BMD was associated with higher subsequent mortality from cardiovascular disease (RR: 2.3; 95% CI: 1–5.3) compared to all-cause mortality (RR: 1.4; 95% CI: 1–2). Similar results were obtained when the participants were distributed into BMD quartiles. A faster rate of hip BMD loss in elderly women was significantly associated with death due to coronary heart disease (RR: 1.3; 95% CI: 1–1.8) or lung disease (RR: 1.6; 95% CI: 1.1–2.5).

8. Pathophysiological hypotheses

Although none of the current hypotheses seems to prevail, several studies showed an increase in cardiovascular deaths among individuals with low BMD values [4,12,15]. Furthermore, the prevalence of cardiovascular disease was higher in patients with osteopenia or osteoporosis than in individuals with normal BMD values [16]. One of the mechanisms underpinning this association is the release by atheroma plaque of proinflammatory cytokines (IL-1, IL-6, and TNF), whose concentrations also increase after the menopause. Furthermore, the cell population in atheroma plaque includes osteoblast-like calcifying vascular cells. The stronger association in women than in men is consistent with data on the association between low BMD and mortality. Nevertheless, this hypothesis cannot fully explain the association. More generally, skeletal health is a fairly good marker for overall health status, and many chronic diseases of a highly diverse nature are associated with a decrease in

BMD. This mechanism might contribute to the association linking low BMD and mortality, but no formal proof is available.

9. Salient points

Over time, evidence has accumulated that a decline in BMD and, to a lesser extent, a fast rate of bone loss are associated with a higher risk of death. In most studies, this association was similar in females and in males. Although few studies assessed causes of death, there is some evidence of a link between low BMD and cardiovascular deaths, which is biologically plausible. The strength of the association between low BMD and higher mortality is modest. Finally, in the few studies that assessed the potential effects of both low BMD and fractures, fractures were consistently a stronger predictor of death [13].

Disclosure of interest

The author declares that he has no competing interest.

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