Pitfalls in interpreting interventional studies for osteoporosis

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Summary

After adulthood, changes in the skeleton are slow and takes years for accruing or losing any appreciable amount of bone mass. Proper interpretation of studies that evaluate the effect of nutrients (like calcium, vitamin D) and anti-resorptive agents (like bisphosphonates) on bone mass is important so that the true effect of the agent is measured correctly. In this report, we are highlighting two issues of utmost importance for correctly interpreting interventional studies for osteoporosis. One issue is the bone remodelling transient (BRT). It refers to a transient change in bone mineral density (BMD) by any agent that reduces remodeling space temporarily. This change is, however, not sustained for a long period and can be misinterpreted as a true gain in bone mass. The second issue is difference between calcium balance and bone balance. Calcium balance is the difference between the amount of calcium ingested in a day and the amount of calcium lost in that day. Recommendations for dietary calcium intake are based on calcium balance studies that presume calcium balance as an equivalent for bone balance. However, these are two different entities and need to be distinguished. Dietary calcium requirements should be established by bone balance studies using bone densitometry, not by calcium balance studies.

KEY WORDS: bone remodeling space; bone remodeling transient; interventional studies; calcium balance; bone balance; osteoporosis.

Introduction

Bone turnover is a slow process. It takes years for gaining or losing any appreciable amount of bone mass. Correct interpretation of studies that evaluate the effect of nutrients and anti-resorptive agents on bone mass is important so that the true effect of the agent is measured. For proper interpretation of such studies, two issues are highlighted in this report. Firstly, the concept of bone remodeling transient (BRT). The interpretation of these studies may be misleading if the BRT is not considered while designing the studies. The second issue is that calcium balance is presumed to be equivalent to bone balance. Dietary calcium intake recommendations are based on calcium balance studies. However, the two processes are different and calcium intake requirements need to be determined by bone balance studies.

Bone remodeling transient

During the remodeling process, sites where remodeling is occurring contain areas where a temporary loss of bone occurs during the resorption phase. This is called remodeling space. This remodeling space is largely demineralised and is not detected by densitometry. Intervention by any anti-resorptive agent like calcium or bisphosphonate reduces this remodeling space (Figure 1), and leads to transient increase in bone mineral density (BMD). This is called bone remodeling transient (BRT). This increase in temporary BMD in one remodeling cycle (early-phase gain) does not reflect true bone gain; nor does this predict the effect of any agent on steady-state bone balance (late-phase gain) (1). The results of any intervention for bone mass would be misleading if the bone density is simply measured without considering the effects of BRT.

In the interventional studies wherein calcium supplements are initiated, serum calcium levels increase slightly and parathyroid hormone (PTH) levels decline. This results in a temporary decline in bone turnover. Bone density increases for the first remodeling cycle, probably as a result of reduction in the remodeling space. After first remodeling cycle, bone density starts declining again. Aloia et al. considered the concept of BRT in a study wherein postmenopausal women were supplemented with calcium (total daily intake 1200-1500 mg). Over the two-year period, there were statistically significant declines in BMD at each site except the lumbar spine. However, when the first year of data was analysed separately, an increase was seen at all sites. The significant change over the first year consisted of two stages: a highly significant increase over the first six months and a relative lack of change from six to twelve months. During the second year, significant decreases were seen in BMD measures (except for the lumbar spine). The transient increase in BMD at the six-month measurement was paralleled by a corresponding increase in serum calcium and a statistically significant decline in PTH, c-terminal telopeptide (CTX) and osteocalcin. By the end of the BRT, when serum calcium and PTH levels reached a steady state (12 months), CTX and osteocalcin were no longer reduced, and levels rose above baseline. BMD resumed its post-menopausal downward trend and BMD was lost from all sites (except the spine) (2). In conclusion, failure to consider the BRT may result in incorrect conclusions not only in calcium supplementation studies, but also in any interventional agent

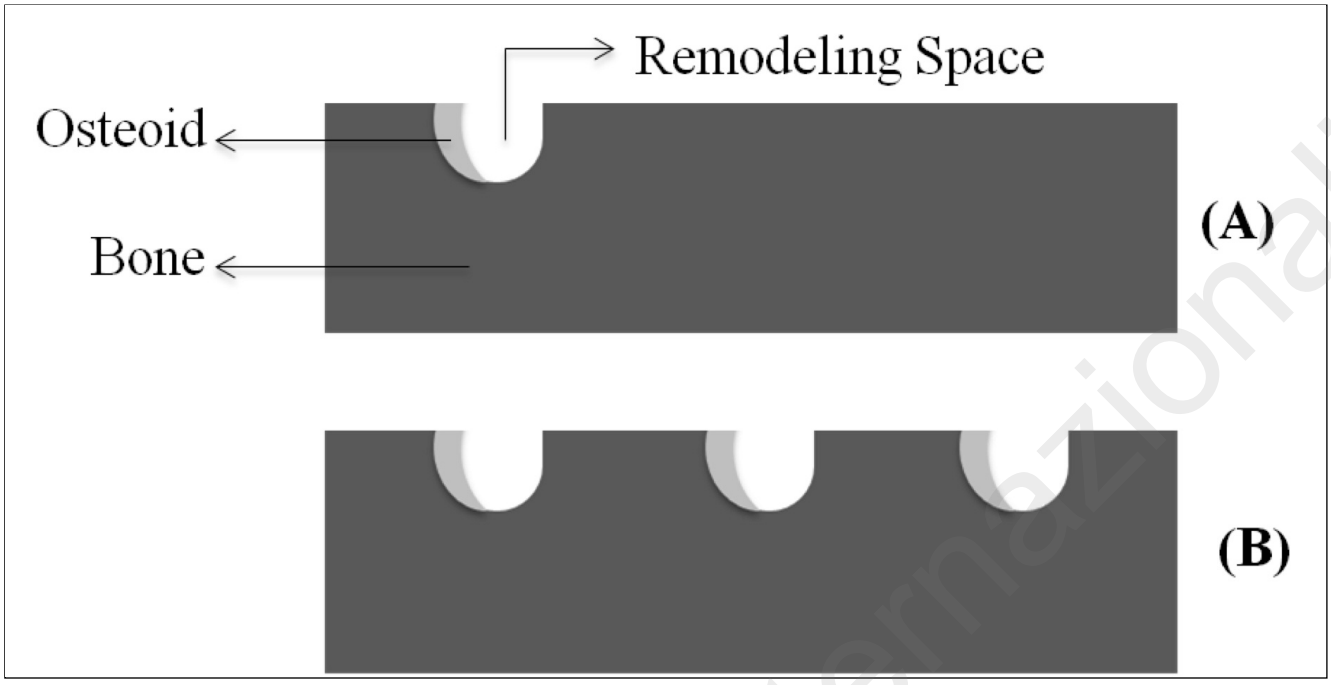

Figure 1 - Two equal volumes of bone showing different remodeling spaces. Panel B has three times the remodeling space as that of panel A. Anti-resorptive agents temporarily decrease this remodeling space and thereby increase measurable BMD.

that temporarily reduces the remodeling space. To reduce the effect of the BRT on interventional study outcomes, it is necessary to study changes that occur during the first remodeling cycle separately from those that occur subsequently. This period is approximately 6 months in postmenopausal women and depends upon the rate of bone turnover, which in turn is influenced by many factors like age, estrogen status, among others (1).

Calcium balance *versus* bone balance

In the normal adult skeleton, the processes of bone resorption (carried out by active osteoclasts) and bone formation (carried out by active osteoblasts) are in dynamic equilibrium, maintaining a constant amount of bone. Bone balance is required to maintain structural integrity of the bone. On the contrary, calcium balance is the difference between the amount of calcium ingested in a day and the amount of calcium lost in that day, principally through excreta (plus small losses through shed hair, skin, nails, sweat and other body secretions). While calcium is found in all tissues, more than 99% of body calcium is found in skeleton. Therefore, it is assumed that the total body calcium balance reflects bone balance. Thus, positive calcium balance would mean that the body is adding bone; zero balance reflects bone equilibrium; and negative balance reflects bone loss. But this is over-simplification. For example, calcium can get accumulated in extra-osseous tissues like vascular system. Furthermore there is ongoing loss of bone in postmenopausal skeleton even in a state of positive calcium balance.

Many professional organisations have made recommendations for optimal calcium intakes based predominantly on the results of calcium balance studies (3), including the recommendations from the Institute of Medicine in 2010 (4). Heaney et al. in 1977 evaluated calcium balance in 130 women aged 35 to 50 years (5, 6). They demonstrated that daily calcium intake associated with zero balance was about 1500 mg in untreated postmenopausal women. Thereafter 1500 mg of calcium became a generalised recommendation to all postmenopausal women. Hunt and Johnson in 2007 examined data from a series of balance studies, which together included 73 women aged 20-75 years and 82 men aged 19-64 years (7). The daily calcium intake predicted to produce a neutral calcium balance was 741 mg, regardless of age or sex. This was about half the amount of calcium required for zero balance as demonstrated by Heaney et al., reflecting some inherent problems with calcium balance studies. Hunt and Johnson concluded that calcium balance was highly resistant to a change in calcium intake across a broad range of typical dietary calcium intakes (415-1740 mg per day; between the ~25th and >99th percentiles of typical calcium intake for all female children and adults aged ≥9 year). Hence, homeostatic mechanisms for calcium metabolism are functional across a broad range of typical dietary calcium intakes to minimise calcium losses and accumulations.

The introduction of bone densitometry has allowed the accurate measurement of bone density, which also predicts fracture risk (8). Bone densitometry demonstrates that there is ongoing loss of bone in postmenopausal women even with high calcium intakes (9). By contrast, calcium balance studies suggest that calcium intakes >1500 mg in postmenopausal women are associated with positive calcium balance (3) and that an intake of 2000 mg per day achieves a positive balance of 460 mg per day (10). If this were correct, this would result in a doubling of total body calcium over a period of several years. Thus, calcium balance does not appear to reflect bone balance. The sequential measurement of BMD using dual energy X-ray absorptiometry (DEXA) over time, that permits the direct assessment of bone balance, would be a better modality for measuring the effect of various nutrients including calcium on bone balance.

Conclusion

Bone remodeling transient is a temporary increase in bone mass caused by any agent that reduces remodeling space. This gain in bone mass is sustained only for a period of one remodeling cycle. The effect of any agent on bone mass may be misinterpreted if BRT is not given due consideration. Requirements for dietary calcium intake are based on calcium balance studies. Calcium balance is presumed to be same as bone balance. However, the two entities are different. Bone balance, measured by bone densitometry, should be utilised in determining the requirements for dietary calcium.

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