
Clinical Research Article

Diminishing Value from Multiple Serial Bone Densitometry in Women Receiving Antiresorptive Medication for Osteoporosis

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Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; LSC, least significant change.

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Abstract

Context: The value of serial bone mineral density (BMD) monitoring while on osteoporosis therapy is controversial.

Objective: We determined the percentage of women classified as suboptimal responders to therapy with antiresorptive medications according to 2 definitions of serial BMD change.

Methods: This was a cohort study using administrative databases at a single-payer government health system in Manitoba, Canada. Participants were postmenopausal women aged 40 years or older receiving antiresorptive medications and having 3 sequential BMD measures. Women stopping or switching therapies were excluded. The percentage of women whose spine or hip BMD decreased significantly during the first or second interval of monitoring by BMD was determined. Suboptimal responder status was defined as BMD decrease during both monitoring intervals or BMD decreased from baseline to final BMD.

Results: There were 1369 women in the analytic cohort. Mean BMD monitoring intervals were 3.0 (0.8) and 3.2 (0.8) years. In the first interval, 3.2% and 6.5% of women had a decrease in spine or hip BMD; 8.0% and 16.9% had decreases in the second monitoring interval; but only 1.4% showed repeated losses in both intervals. Considering the entire treatment interval, only 3.2% and 7.4% showed BMD loss at spine or hip. Results may not apply to situations of poor adherence to antiresorptive medication or anabolic therapy use.

Conclusion: Among women highly adherent to antiresorptive therapy for osteoporosis, a very small percentage sustained BMD losses on repeated measures. The value of multiple serial BMD monitoring to detect persistent suboptimal responders should be questioned.

Key Words: Bone density, osteoporosis, bisphosphonates, DXA, GK, SM, SF, LL and WL have nothing to declare

The prevention of osteoporosis-related fractures is important for individuals at high fracture risk and effective pharmacotherapies exist for this purpose (1). Although antifracture therapies reduce fractures in groups of patients (2, 3), it can be challenging to assess an individual patient's response to therapy (4). Occurrence of fracture while on treatment is an outcome-oriented approach to monitoring therapy but confounded because no treatment can prevent all fractures (5) and fracture is not a direct marker of a drug's effect on bone metabolism.

Given its traditional role in osteoporosis screening, bone mineral densitometry (BMD) has been used for risk prediction and therapy monitoring. Serial BMD monitoring while on therapy is intuitive for physicians and patients who are accustomed to repeated measures of biomarkers for monitoring progress. Clinical trials of antifracture therapies report average BMD change (6, 7) since available therapies result in net BMD increase averaged across the treated population. BMD improvement has been proposed as a surrogate endpoint for fracture in drug development since meta-regression of clinical trials show that larger improvements in BMD in a treated population compared with an untreated population are associated with greater reductions in fracture risk (8). Many clinical practice guidelines recommend serial BMD testing for this purpose (9, 10, 11).

No trial has directly tested whether BMD monitoring in practice improves fracture outcomes. Observational data reported that BMD loss (versus stable BMD, over a mean interval of 4.5 years) in women receiving antifracture treatment was associated with increased fracture risk (12). Using propensity score matching, the same group reported that a repeat BMD test within 5 years of starting treatment was associated with lower fracture risk and greater medication persistence than in those who were not monitored (13). However, recent evidence from the Women's Health Initiative has cast doubt upon the ability of serial BMD to discriminate between postmenopausal women who ultimately will or will not fracture (14).

Several factors may limit the reliability and clinical applications of observed change in BMD (15, 16, 17, 18, 19, 20). An underappreciated issue has been the problematic comparison of mean BMD change data as published in clinical trial reports to that of the individual patient on treatment. Reports of mean BMD change in study populations necessarily hide

the actual inter- and intra-individual variance in BMD change such that physicians may incorrectly assume that deviation from the expected population average may be interpreted as indicative of a problem with therapy.

We sought to define the spectrum of serial BMD change within a clinical practice population highly adherent to continuous antiresorptive treatment. The primary hypothesis was that among treatment-adherent women who do not switch therapies, multiple serial BMD measures rarely identify suboptimal responders.

Materials and Methods

Population

We used a large BMD registry in Manitoba, Canada, to derive a cohort of postmenopausal women who initiated continuous antiresorptive osteoporosis therapies and who underwent 3 BMD tests during treatment years. The Manitoba database is drawn from the population of 1.3 million persons who undergo BMD measurement with dual-energy x-ray absorptiometry (DXA) at centralized facilities within a province-wide government health system (21). This population-based BMD registry, with a completeness and accuracy rate of 99%, is linked to provincial healthcare data, including prescription drug data, available for Manitoba residents beginning in the 1995/1996 fiscal year (22).

The study cohort comprised postmenopausal women aged 40 years or older who had a baseline BMD followed by initiation of antiresorptive medication and then underwent 2 subsequent DXA examinations without medication switching from the first to final BMD. The first interval was from medication start to first follow-up BMD and the second interval was from first follow-up BMD to second follow-up BMD. We excluded women stopping or switching therapies, and also women receiving treatment at the time of the first DXA examination. Cohort participants were those with BMDs performed between January 1, 1996, and March 31, 2018. Antiresorptive medication use was defined by a dispensation for a bisphosphonate (oral or intravenous), calcitonin, raloxifene, denosumab, or systemic estrogen. For each interval, we identified the total number of days that medications were dispensed and the actual therapeutic agent dispensed. We calculated the

medication possession ratio for each interval as the sum of the days' supply for all dispensations of a specific drug in an interval, divided by the total number of days in the interval.

Bone Densitometry

Lumbar spine and hip BMD scans were performed according to manufacturer recommendations. The instruments used for this study exhibited stable long-term performance (coefficient of variation <0.5%). All reporting radiologists and supervising technologists maintain certification with the International Society for Clinical Densitometry. The absolute difference between paired BMD tests (in g/cm^2) was determined applying 95% least significant change (LSC) values for assessment of change, where LSC is the least amount of BMD change that can be considered statistically significant at $P < .05$ (23, 24, 25). LSC was calculated from more than 400 DXA scan pairs as previously reported (26) and the 95% LSC values were within acceptable ranges (25): total hip, $0.03 \text{ g}/\text{cm}^2$; lumbar spine, $0.05 \text{ g}/\text{cm}^2$. A difference less than these amounts was designated as stable (unchanged); an increase or decrease exceeding these amounts was denoted as a significant increase or decrease in BMD. All DXA acquisitions were reported as part of routine clinical practice; measurement sites deemed invalid for interpretation (eg, due to extensive degenerative change) were excluded. For study inclusion, each cohort member had to have at least 1 BMD site (hip or spine) that yielded 3 serially comparable images and measurements spanning the entire study timeframe. The 10-year estimated fracture risk reported with each bone density reading was derived according to the FRAX® tool, Canadian version.

Study Measures and Analysis

Three monitoring intervals were constructed for each cohort member (1): first to second BMD (ie, first interval) (2), second to third BMD (ie, second interval), and (3) first to third BMD (total interval). BMD change was calculated for each interval.

The percentage of cohort members with a significant BMD decrease in any interval was calculated. Next, patients were classified according to the direction of change in each interval: stable, increased, or decreased. Individuals were further classified whether the direction of change was the same in both the first and second intervals. Finally, we calculated the percentage of patients who would be considered treatment suboptimal responders according to 2 definitions: (1) those with significant BMD decreases in both monitoring intervals, or (2) those in whom there was significant BMD loss in the total monitoring interval.

All analyses were performed using lumbar spine and hip BMD as independent measures under the assumption that a decrease in either spine or hip would draw attention in clinical practice.

The study cohort was described using mean and 95% CI for continuous measures and frequencies and percentages for categorical measures. Chi-squared tests of association were used to compare proportions. Pearson correlation coefficients were used to compare BMD change as continuous measurements. All analyses were performed using MedCalc Statistical Software version 19.0.7 (MedCalc Software bvba, Ostend, Belgium) and Statistica version 13.0 (StatSoft Inc, Tulsa, OK); $P < .05$ was deemed to represent a statistically significant result.

Results

We identified 12 256 women with 3 sequential BMD records; 10 887 were excluded according to the inclusion/exclusion criteria yielding a final analytic cohort of 1369 women; 1176 had 3 serial spine BMD measurements and 1330 had 3 serial measurements at the total hip site (Fig. 1). The population characteristics are shown in Table 1; the mean (SD) age was 62.9 (9.0) years and mean (SD) baseline lumbar spine and total hip T-scores were -2.4 (1.2) and -1.7 (1.0), respectively. There were 24.2% of women with prior fracture and 12.6% whose Canadian FRAX® risk estimate (FRAX® Desktop Multi-Patient Entry, version 3.8) suggested a >20% 10-year risk for major osteoporotic fracture. Osteoporosis treatments included alendronate (62.1%), risedronate (10.8%), estrogen (13.5%), etidronate (6.8%), raloxifene (5.9%), or other (calcitonin/denosumab; 0.9%). The mean (SD) medication possession ratio in the first monitoring interval was 0.86 (0.17) and 0.85 (0.18) in the second monitoring interval, consistent with high adherence rates.

The mean (SD) duration of the first monitoring interval was 3.0 (0.8) years and it was 3.2 (0.8) years for the second monitoring interval. For the first monitoring interval, the mean absolute change in spine BMD was $+0.042 \text{ g}/\text{cm}^2$ (95% CI 0.039-0.045) and $+0.022 \text{ g}/\text{cm}^2$ (95% CI 0.020-0.023) at the hip. In the first interval, there was a statistically significant increase (exceeding the 95% LSC) for spine BMD in 43.6% and for total hip BMD in 41.0% of the women, while 3.2% and 6.5% had a significant decrease in the BMD sites respectively. For the second monitoring interval, the mean absolute change from the second BMD measurement was $+0.009 \text{ g}/\text{cm}^2$ (95% CI $+0.006$ to $+0.012$) for the spine and $-0.006 \text{ g}/\text{cm}^2$ (95% CI -0.008 to -0.004) at the hip. There was a statistically significant increase in the second interval for spine BMD in 16.3% of the women and for total hip BMD in 8.6% of the women, while 8.0%

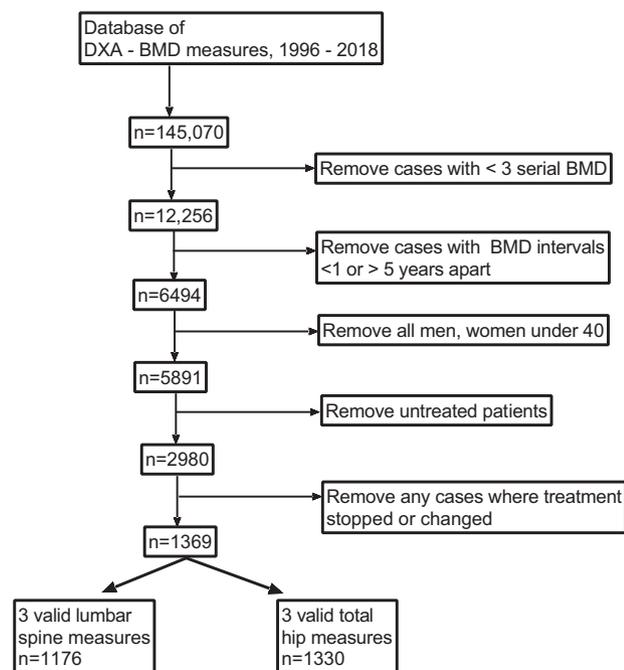


Figure 1. Study population flow chart.

Table 1. Population characteristics

Parameter	Result (mean, SD)
Age ^a	63.1 (9.1)
Lumbar spine BMD T-score ^a	-2.4 (1.2)
Total hip BMD T-score ^a	-1.7 (1.0)
10-year major osteoporosis fracture risk ^a	11.0 (6.7)
10-year hip fracture risk ^a	2.6 (3.4)
Interval, visit 1 to visit 2, years	3.0 (0.8)
Medication possession ratio, visit 1 to visit 2	0.86 (0.17)
Interval, visit 2 to visit 3, years	3.2 (0.8)
Medication possession ratio, visit 2 to visit 3	0.85 (0.18)

^aAt visit 1.

and 16.9% of women had a significant decrease at the 2 sites, respectively. There was a statistically significant positive correlation between spine and hip BMD change during the first monitoring interval ($r = 0.44, P < .001$), but no statistically significant correlation in BMD change between the first and second intervals for the spine ($r = -0.04, P = .14$) or hip ($r = -0.03, 0.31$).

The direction of any significant BMD change at the spine and total hip in each cohort member between the first and second monitoring intervals is shown in Figs. 2 and 3. At the spine, of 1136 women whose first interval BMD was stable or increased, 94 women (8.2%) were reported as having a BMD loss in the second interval. Fewer than 6 women (<0.5%) had a lumbar BMD loss documented during both intervals. At the hip site, of 1243 women whose first interval BMD was stable or increased, 203 (16.3%) were reported

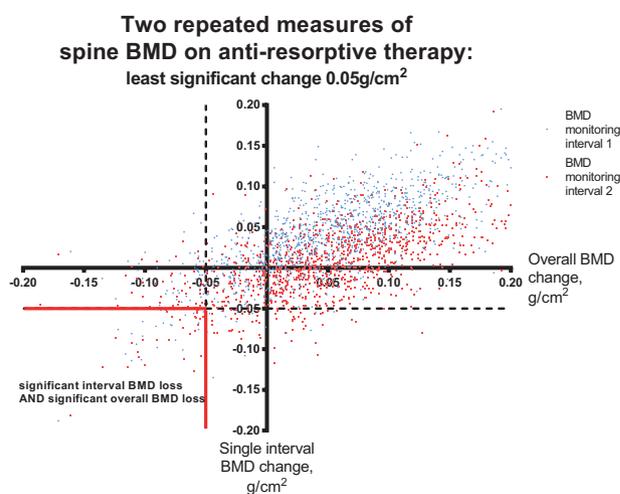


Figure 2. Scatterplot of paired serial spine BMD measures in antiresorptive treated patients according to absolute magnitude of measured change in discrete follow up intervals, compared to long-term overall change. Measured BMD loss exceeding the LSC of 0.05 g/cm² (denoted by the dashed lines) is statistically significant. Results appearing in the lower left, red-lined quadrant represent patients in whom a significant interval BMD loss was associated with a sustained long-term BMD loss. LSC = least significant change, BMD = bone mineral density.

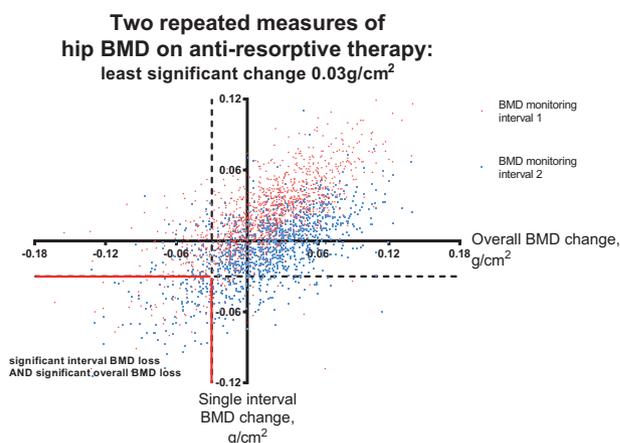


Figure 3. Scatterplot of paired serial hip BMD measures in antiresorptive treated patients according to absolute magnitude of measured change in discrete follow up intervals, compared with long-term overall change. Measured BMD loss exceeding the LSC of 0.03 g/cm² (denoted by the dashed lines) is statistically significant. Results appearing in the lower left, red-lined quadrant represent patients in whom a significant interval BMD loss was associated with a sustained long-term BMD loss. LSC = least significant change, BMD = bone mineral density.

as having a BMD loss in the second monitoring interval but only 18 women (1.4%) showed repeated losses across both the first and second monitoring intervals. In a sensitivity analysis restricted to women using exclusively potent oral bisphosphonates (alendronate, risedronate; $n = 1038$) we noted no difference in the percentage of women reported as losing significant bone density in both measurement intervals ($P = .8$).

With respect to overall BMD change from first to final BMD, 6.5% of women on antiresorptive therapy had a significant decrease in spine BMD and 13.4% had a significant decrease in hip BMD. The direction of BMD change in the first interval after treatment initiation compared with the long-term BMD change while on therapy revealed that among those whose first interval spine BMD was significantly decreased, 15/40 (37.5%) ultimately had a stable or increased long-term result without therapy change. For those with first interval decreased at the total hip, 24/87 (27.6%) ultimately had stable or increased long-term BMD without change in therapy. Conversely, 51/1135 (4.5%) of women with stable/increased spine BMD at the end of the first interval ultimately had a significant overall loss by the final BMD compared with baseline. For the total hip site, 116/1243 (9.2%) had a reassuring result at the first interval BMD yet ultimately sustained a significant overall loss by the final BMD.

Discussion

Using a large registry that captures serial BMD changes in postmenopausal women using antiresorptive medications with high adherence rates in the routine clinical practice setting, we found only 1% of women showed repeated bone loss on 2 sequential BMD monitoring tests. BMD gains during the first monitoring interval were larger than those seen during the second monitoring interval.

The value of any osteoporosis therapy monitoring test should be evaluated by determination of fracture outcome rates with respect to various observed changes in surrogate biomarkers and subsequent changes to management. Post hoc analyses of clinical trials and observational studies have provided mixed evidence to support the concept that repeat BMD performed while on therapy can predict better or worse outcomes for individual patients (2, 13, 27, 14). In the absence of clearer evidence in support of monitoring practices, some guidelines have suggested abandoning BMD monitoring of osteoporosis therapy altogether (28).

Nevertheless, both patients and physicians highly value a BMD monitoring approach to therapy (29) and the BMD response to treatment with antiresorptives is routinely viewed as a marker of therapy success. The Endocrine Society guideline considers a loss of BMD greater than the LSC as “failure of therapy” (9) but this strategy, applied in our population, would mean that up to 25% of treated women would be suboptimal responders according to whether a statistically significant BMD loss was seen at some point over the course of multiple examinations, despite the fact that only 10% or less would have a net loss across the whole treatment course and less than 2% would have statistically significant losses in each of 2 serial testing

intervals. The International Osteoporosis Foundation position statement on osteoporosis treatment failure takes a more conservative approach, requiring a combination of fracture on therapy in addition to large, adverse changes in a monitored parameter (BMD or bone turnover marker) (30). However, a single monitoring BMD may still be useful for the purpose of identifying patients who will be predicted to derive less benefit from their therapy or for enhancing patient medication adherence, namely in those for whom BMD decreases on therapy (29).

Our findings are not entirely unique and Fig. 4 outlines some of the main observations relevant to this debate; 20 years ago, Cummings et al. published a patient-level analysis of serial BMD changes among women in pooled data from alendronate and raloxifene clinical trials (31). They showed a phenomenon of often contradictory BMD changes across 2 annual monitoring intervals which was interpreted at the population level as “regression to the mean.” The individual patient relevance of that study has been criticized (32) as being an epiphenomenon arising within any serial measures in a population, but our data support that serial BMD monitoring in clinical practice is accompanied by uncertainty about the value of additional BMD monitoring performed after the first monitoring interval. It is not necessarily an issue of treatment efficacy ascertainment so much as an issue of unreliable and sometimes contradictory signals when viewed in the real-world sequence of their occurrence. Given previous evidence that suggests a benefit still exists among treated patients despite losses in BMD on therapy (33, 34), our data suggest that therapy switch may not always be required and the first response to a decrease in BMD should be a review of medication adherence. Our study adds to previous studies which have shown that multiple repeat BMD tests are of limited value. The present analysis looks at such use in the context of ongoing treatment; other studies have drawn similar conclusions in the context of long-term fracture risk prediction—the first BMD is usually the most important of all measures (35).

The strengths of our study include use of a well-characterized, longitudinal BMD registry of women whose DXA measurements were conducted within a centralized program, reflecting real-world clinical practice. Comprehensive data on medication usage permitted us to derive the cohort of interest by allowing exclusion of those in whom changing therapies would have otherwise been a major confounding variable.

A study limitation is its retrospective nature and the fact that BMD change, rather than fracture, was the outcome of interest. Given our narrowly defined inclusion criteria, the study was underpowered to assess fracture outcomes. The use of net BMD change from 2 sequential BMD measurements answers some of the prior

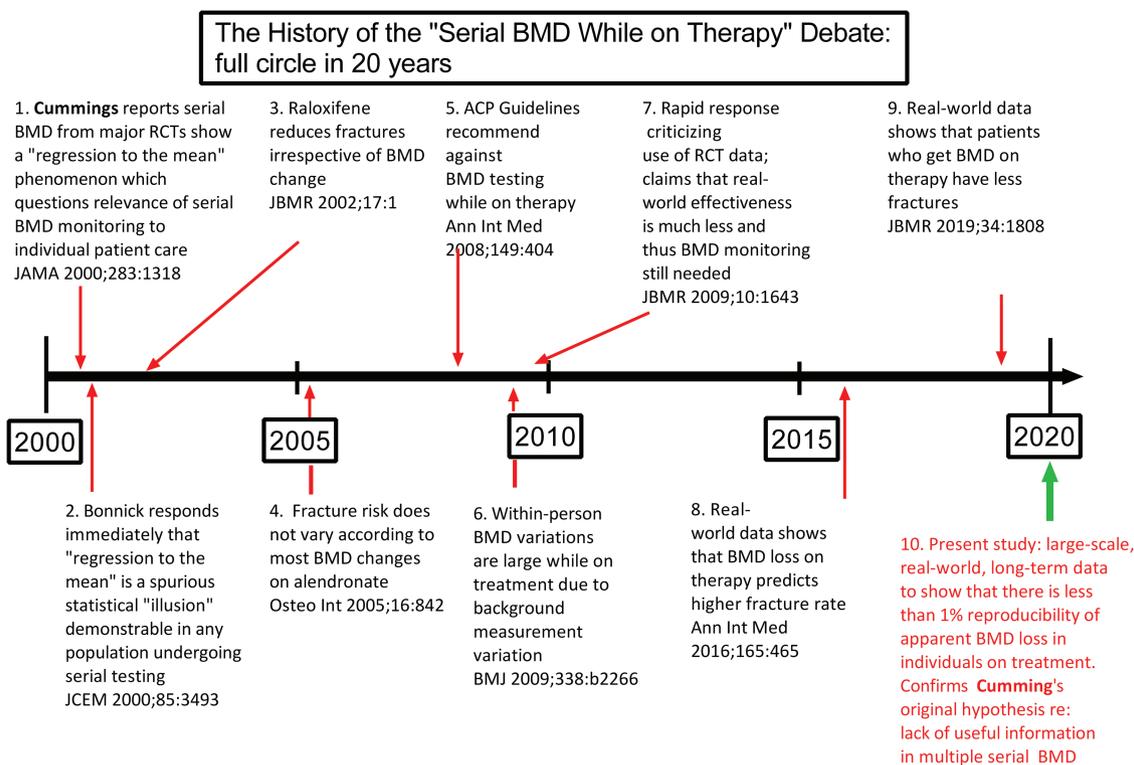


Figure 4. Timeline of key observations and studies pertaining to the use of serial BMD measures among antiresorptive-treated osteoporosis patients.

objections to a "regression to the mean" interpretation (32) and serves as a reasonable surrogate for a patient who is truly failing to respond to antiresorptive therapy. Our cohort was selected for long term high-degree adherence to antiresorptive therapy; therefore, the present data cannot be applied to patients in whom treatment adherence is suspected to be suboptimal or unknown. Lastly, our data cannot be considered relevant to patients with severe low bone densities, those using anabolic osteoporosis therapies, those with special secondary bone disorders (ie, transplant), or those in whom a complex, treatment-switching paradigm is in use. Our data cannot be assumed to be relevant to questions of monitoring patients on a bisphosphonate hiatus although a similar, future analysis in that population would be of value.

In summary, only about 1% of all antiresorptive treatment-adherent women actually have repeated, progressive BMD losses when 3 sequential BMD measurements are considered. A repeat BMD after starting antiresorptive therapy may identify a small subset of women losing BMD and therefore at higher risk of fracture, but the value of routine, serial BMD monitoring thereafter must be questioned.

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Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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