Review

Bone turnover markers and prediction of bone loss in elderly women

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Abstract

Around 70,000 osteoporosis-related fractures occur in Sweden annually and approximately half of the women in western world will sustain a fragility fracture after the age of 50 years. Fracture preventive efforts require the identification of individuals who are at high risk. Biochemical markers of bone turnover (BTMs) have shown some degree of fracture predictability. There is also a correlation between rate of decrease of areal bone mineral density (aBMD) and incident fractures.

In this study, the correlation between BTMs and rate of bone loss (change of aBMD and ultrasound variables) over 5 years was investigated in the Malmö OPRA cohort of 75-year old women (n = 506 to 601). In addition, correlation of BTMs and bone metabolism, as assessed by scintigraphy, was tested in postmenopausal women (n = 22). Finally, the effect of precision error on the longitudinal monitoring of change in aBMD was assessed in elderly women (n = 690) and in elderly men (n = 211).

There was a strong correlation between all bone turnover markers and the results of scintigraphy (total skeletal uptake of ^{99m}Tc-labelled methylene diphosphonate), with no significant difference between the markers of bone formation bone resorption. BTMs were correlated to the 5-year rate of change of aBMD, especially in the legs and the total body, and 5-year change in speed of ultrasound. When serial measurements of BTMs were analysed, the mean value of measurements were correlated more strongly to aBMD change than single measurements, and women with constantly high levels of BTMs had higher rates of bone loss. Precision error of aBMD measurement by dual-energy X-ray absorptiometry has an influence on the detection of individuals with aBMD change exceeding the least significant level. The calculated follow-up interval for detection of a change in aBMD beyond the least significant level in more than half of the elderly individuals ranged from 3–32 years, and was dependent on the equipment used and the skeletal site tested.

The results of this study indicate that currently available BTMs are associated with future bone loss. However, these correlations may not be strong enough to be predictive of bone loss at the individual level. DXA also has some limitations when used in the longitudinal setting in elderly individuals. DXA is therefore of limited use in the longitudinal monitoring of bone loss. Further studies with novel bone turnover markers may improve the ability of BTMs to predict bone loss.

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This study was performed in Malmö University Hospital, Lund University, Sweden and the results were included in a thesis with five published papers for a PhD degree with the Lund University, Sweden and defended the thesis on 23rd of October 2009.

Introduction

Bone is a dynamically and metabolically active organ that is continuously subjected to resorption and formation by coordinated action of osteoclasts and osteoblasts on the surface of trabecular bone and in the Haversian canals (1). These two processes are collectively called bone turnover or bone remodeling and they are coupled in time and space. About 10 % of the skeleton is remodeled each year (2), allowing the skeleton to adjust its strength to mechanical stress and to repair any microdamage (3, 4). Bone remodeling is also necessary for maintaining the metabolic function of the skeleton and calcium homeostasis (5).

During the growth period in childhood and in adolescence bone formation predominates; increasing the bone size and strength until the maximum bone mass (peak bone mass) is reached in the 2nd or the 3rd decade of life (6, 7). After reaching the peak bone mass, there is a state of equilibrium, where the rate of bone formation equals the rate of bone resorption. After the age of 40 years the bone resorption starts to predominate over formation. The aging process

includes endosteal resorption, periosteal apposition, trabecularization of cortical bone and increase in cortical porosity. In women this process is accelerated in the first few years after the menopause due to estrogen deficiency (8). Postmenopausal women decrease the aBMD or lose bone at a rate of 2-5% per year (8). Individuals who lose bone at a fast rate can develop osteoporosis and get fragility fractures at early ages.

Osteoporosis is a systemic skeletal disease characterized by low bone mass, micro architectural deterioration of bone tissue leading to increased risk of fragility fracture, most commonly affecting postmenopausal women and elderly men. After 50 years of age more than 40% of women and 13% of men in western countries are at a risk of developing a fragility fractures at any site during the rest of their life time (9). Osteoporosis is diagnosed by measuring bone mineral density (aBMD) using dual energy X-ray absorptiometry (DXA) and defined as aBMD value 2.5 standard deviations or more below the mean of young female adult population. It is important to identify individuals with osteoporosis and individuals with fast bone loss to take preventive measures to avoid fractures. Fast bone losers are detected using DXA, measuring aBMD at least one to two years apart. It is expensive and consumes time during which the woman loses bone further.

Bone turnover markers, (BTMs) or biochemical markers of bone turnover, are bone tissue proteins or their fragments, or enzymes released from bone cells during bone turnover. Proteins can be by-products of collagen formation or products of collagen degradation, or non-collagenous proteins such as osteocalcin or bone sialoprotein. Enzymes, such as bone-specific alkaline phosphatase and tartrate-resistant acid phosphatase 5b, can also be used as bone turnover markers. Bone turnover markers can be detected in serum or urine. Ideally, they should reflect only the activity of osteoblasts or osteoclasts. Bone turnover markers that are released predominantly during bone formation or resorption are known as bone formation or resorption markers, respectively (10). Bone formation and bone resorption are usually tightly coupled in time and space and therefore, any marker reflects the overall rate of bone turnover (11). Certain bone turnover markers may reflect different stages of formation and resorption but they cannot reflect disease-specific processes or for instance distinguish between the activities at cortical or trabecular bone (11).

The main objective of this study was to investigate the possibility of predication of bone loss over five years using baseline levels of BTMs as well as a serial measurement of BTMs. The effect of precision error of DXA measurements on the assessment of repeated bone densitometry in elderly women and men was also studied. In the first study it was aimed to study whether bone turnover, as assessed by total skeletal uptake of Technetium 99-labelled methylene diphosphonate, correlate more to bone formation markers or to resorption markers.

Materials and methods

These studies were conducted in Malmö University Hospital, Lund University, Malmö in Southern Sweden.

Participants in Study I

For this study (12) we recruited 22 post menopausal women (aged 52–80 years) out of the women who sought medical advice or treatment for minor orthopaedic problems, and who were free from the condition that had originally brought them to the clinic, from the registers of the orthopaedic clinic at Malmö University Hospital, Sweden. By the time the study was started, the women who had ever been treated with bisphosphanates or women who had been treated with oestrogens or corticosteroids within the previous year and women with bone active disease were excluded.

Participants from the Malmö OPRA cohort, Study II–V

The Malmö Osteoporosis Prospective Risk Assessment (OPRA) cohort consisted of elderly women who were randomly recruited from the population registry of Malmö city (13-16). For the baseline investigation, 1604 women were invited by mail one week after their seventy-fifth birthday. Baseline recruitments took place between November 1995 and May 1999. Of the 1,604 women invited, 1,044 (65%) participated at baseline. Of the 560 women who did not participate, 13 had died shortly after the invitation, 139 could not come because of illness, 376 were not interested or could not attend for reasons other than illness, and 32 women could not be reached despite repeated letters and telephone calls. Baseline DXA was performed on 995 individuals. The women were invited for prospective follow-up visits after 1, 3 and 5 years. At the 5-year follow-up, 691 had second aBMD measurements performed at least one site, and 551 women had completed both baseline and 5-year quantitative ultrasound scan (QUS) measurements.

In **Study II,** 601 women who had attended both the baseline and the 5-year DXA measurements were included (13). These women had baseline serum and/or urine samples available and had not taken hormone replacement therapy or bisphosphonates during the study period.

In **Study III,** 506 women who had attended both the baseline and the 5-year Quantitative Ultrasound Scan of calcaneus (QUS) measurements were included (14). These women had baseline serum and/or urine samples available and had not taken hormone replacement therapy or bisphosphonates during the study period.

In **Study IV,** 573 women were included (16). They attended both the baseline and the 5-year DXA measurements, and had given serum and/or urine samples at baseline and at the 1, 3 and 5-year follow up measurements. The women included had not taken hormone replacement therapy or bisphosphonates during the study period.

In Study V, 691 women were included (15). These women had a baseline and 5-year follow-up DXA measurements available. In addition, 211 men from the Malmö part of the MrOs study (the Osteoporotic Fractures in Men Study) who attended DXA measurements at baseline and at the 5-year follow-up were included. The MrOs study is an international multi-centre study on risk factors for osteoporosis and fracture in elderly men. The men in the Malmö cohort of the MrOs study were recruited from the population registers of Malmö city.

Bone density measurements

Dual-energy X-ray absorptiometry

The total body, the total hip, the femoral neck and the lumbar spine aBMD and bone mineral content (BMC) measurements in the women were performed by using a Lunar DPX-L scanner (Lunar DPX-L; Lunar Corporation, Madison, USA) at baseline (**Study I–V**) and after 5 years **(Studies II, III, IV and V)**. Men were measured at the same regions of interest using a Lunar Prodigy scanner (Lunar Prodigy, Madison, USA), which uses the fan beam technique.

Quantitative ultrasound of the calcaneus

Ultrasound measurements were performed in elderly women at baseline and after five years with a Lunar Achilles® scanner (Lunar Corporation, Madison, USA) for the right calcaneus. The results were obtained as speed of sound (SoS), broadband ultrasound attenuation (BUA) and the stiffness index **(Study III)**.

Serum and urine samples

Serum and urine samples were collected for the analysis of markers of bone turnover at baseline (age 75 years, **Studies II, III and IV**), and follow-ups after 1, 3, and 5 years (**Study IV**). Non-fasting blood samples were collected between 0800 and 1300 hour, and serum was separated and stored within two hours. First morning void urine samples were also collected. Serum and urine samples were stored at -80°C. For **Study I**, non-fasting serum and urine samples were collected at 0900 hour. The analyses for each bone metabolic marker were done at the same time in order to minimise inter-assay variability.

Measurement of bone turnover markers

Markers of bone formation

Bone-specific alkaline phosphatase (S-Bone ALP) was determined by using Metra BAP immunoassay (Quidel Corporation), with an intra- and inter-assay coefficient of variation (CV) of 3.6% and 4.4%, respectively. Serum intact and N-mid osteocalcin (S-Total OC(N-Mid®)) were determined by using the Elecsys N-MID Osteocalcin Immunoassay (S-Total OC; N-MID®; Roche Diagnostics), with intra- and inter-assay CV of 2.3% and 2.4%, respectively. Serum intact osteocalcin (S-OC[1-49]), serum total osteocalcin (S-Total OC) and serum total carboxylated osteocalcin (S-cOC) were determined by previously described, in-house protocols with intra- and inter-assay CV of less than 5% and 8% respectively, for all the assays (17). Briefly, protocols are two-site assays based on two monoclonal antibodies (Mabs) in the combinations 3G8/2H9 (for S-OC[1-49]), 2H9/6F9 (for S-TotalOC) and 6F9/3H8 (for S-cOC). Mab 3G8 is specific for intact OC, Mab 6H9 binds to fragment Gly^{7}-Arg^{19}, Mab 2H9 recognizes fragment Arg^{20}-Arg^{43} and Mab 3H8 binds to the same fragment (Arg^{20}-Arg^{43}) but prefers OC-containing gamma-carboxyglutamic acid (Gla), with only 9% cross-reactivity with non-Gla-containing OC (18).

Markers of bone resorption

Serum C-terminal cross-linking telopeptides of type I collagen (S-CTX-I) was determined by Elecsys β-Cross Laps® immunoassay (Roche Diagnostics) with intra- and inter-assay CV of 5.9% and 5.8%, respectively. Serum tartrate-resistant acid phosphatase 5b (S-TRACP5b) was assessed by a solid phase, immunofixed enzyme activity assay as described earlier (19) with an intra- and inter-assay CV of 1.8% and 2.2%, respectively.

Urinary deoxypyridinoline (U-DPD) was measured by the Metra DPD Immunoassay (Quidel Corporation, San Diego, CA, USA) with an intra- and inter-assay CV of less than 12% and 10%, respectively.

Urinary osteocalcin

Urinary osteocalcin (U-OC) consists of fragments less than thirty residues in length from the middle region of

the molecule (20). Three assays were used to analyse various molecular forms of U-OC as described previously (21). Assays were based on the same Mabs as the assays for serum OC (18). Briefly, the two-site assay U-MidOC consisted of Mabs 6F9 and 3H8 and recognized the most abundant mid-molecule fragments of U-OC (spanning residues 7–31, 7–29, 6–29, 9–31, 7–32 and 7–33). Two-site assay U-LongOC (2H9/6F9) detects only the longest U-OC fragments (7–32, 7–33) with low affinity. Competitive assay U-TotalOC (3H8) also measures (in addition to the same mid-molecule fragments) more truncated U-OC fragments, starting from residue Asp^{14}. The intra- and inter-assay CVs were 1.7% and < 12% (for U-MidOC), 4.3% and < 14% (for U-LongOC), and 14% and < 27% (for U-TotalOC), respectively (21).

Urinary creatinine

Urinary creatinine was measured by the kinetic Jaffe reaction with a Beckman synchron LX20-4, with CVs of 3% or less. All the measurements of urinary bone markers were corrected for urinary creatinine and expressed as ratios (**Studies I, II, III, and IV**).

Bone Scintigraphy

Bone scintigraphy procedure was performed within 28 days after the DXA scanning (**Study I**) according to a method described by Brenner *et al.* (22). An intravenous injection of 520 (517 ± 15) MBq of ^{99m}Tc-MDP (Medronate®, Amersham International) was given at 0900 hour. Whole body imaging was performed directly (3 minutes) after injection and 5 hours after injection (1400 hour). A double-headed gamma camera system (Siemens Multispect 2) equipped with low-energy high-resolution collimators was used for the scan.

Total skeletal uptake (TSU) of ^{99m}Tc-MDP was calculated using three minute images and five hour images, excluding the urinary bladder and the soft tissue uptake as described by Brenner *et al.* (22).

Results

Results- Study 1

Bone turnover markers are correlated with total skeletal uptake of ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP)

The median TSU of ^{99m}Tc-MDP was 23% (range 5–48%). There was a significant correlation between all bone turnover markers, with r-values from 0.52 ($p = 0.013$) to 0.90 ($p < 0.001$). The two bone resorption markers had numerically higher correlations (S-TRACP5b: r = 0.90; and S-CTX-I: r = 0.80) than the bone formation markers (S-Total OC: r = 0.72; and S-Bone ALP: r = 0.66), but the differences were not statistically significant. There was no correlation between the TSU of ^{99m}Tc-MDP and age, weight, body mass index or total body aBMD.

Results- Study II.

Prediction of bone loss using biochemical markers of bone turnover

Annual change in aBMD varied between +0.4% (spine) and -2.0% (femoral neck). Significant associations ($p < 0.01$) in the aBMD change of the leg region (derived from the total body measurement) were found for four different S-OCs (standardized regression coefficient -0.20 to -0.22), U-DPD (-0.19), S-TRACP5b (-0.19), S-CTX-I (-0.21), two of the three U-OC/crea (-0.16).

After adjustment for baseline total body BMC (bone mineral content), associations were found for all S-OC:s (-0.11 to -0.15), two of the three U-OC:s (-0.14 to -0.16) and aBMD change at the total hip, and for three of the four S-OC:s (-0.14 to -0.15), S-TRACP5b (-0.11), two of the three U-OC:s (-0.14 to -0.15) and aBMD rate of change at the femoral neck. There were no significant associations concerning change in aBMD at the lumbar spine.

Results- Study III.

Bone turnover markers are correlated with quantitative ultrasound of the calcaneus: 5-year longitudinal data

There was a correlation between all markers and baseline QUS measurements ($Beta_{std}$ values from -0.07 [$p < 0.05$] to -0.23 [$p < 0.001$]). When we evaluated the correlations between the baseline bone markers and 5-year prospective changes in QUS, all three molecular forms of serum osteocalcins showed correlations with changes of SoS and stiffness index (unadjusted and adjusted for baseline body weight) ($Beta_{std} = –0.10$ [$p < 0.05$] to -0.17 [$p < 0.001$]). S-CTX-I showed a correlation with changes in SoS (unadjusted and adjusted for weight) and unadjusted stiffness index ($Beta_{std} = –0.09$ to $–0.10$ [$p < 0.05$]). S-TRACP 5b and U-MidOC/crea showed correlations with unadjusted changes in SoS ($Beta_{std} = -0.10$ [$p < 0.05$]). S-Bone ALP did not show any correlation with any of the prospective changes in QUS, and none of the bone turnover markers correlated with prospective changes in BUA before or after adjustment of baseline body weight.

Results- Study IV

Serial assessment of serum bone turnover markers identifies women with the highest rate of bone loss and osteoporosis risk

Baseline BTMs showed a weak correlation with change in total body aBMD, but the association was more pronounced when we used the average of two measurements of each marker (standardised regression coefficient from –0.12 to –0.23, $p < 0.01$). Adding a third and a fourth measurement further strengthened the correlation (with coefficients of up to -0.30, $p < 0.001$). Changes in BTMs did not correlate to bone loss as strongly as the average values. Women with constantly high turnover lost significantly more bone at total body (-2.6%) than women with intermediate (-1.6%) or low turnover (-0.2%, p for trend < 0.001). They also had greater bone loss at the hip (-8.3%, -6.0% and -5.1%, respectively; $p = 0.01$). Results were similar in the subgroup of women with osteopenia.

Results - Study V.

Effect of precision on longitudinal follow-up of bone mineral density measurements in elderly women and men

At baseline, aBMD (SD) in g/cm^2 for women was: total body (TB) 1.008 (0.093), total hip (TH) 0.857 (0.147) and lumbar spine (LS) 0.987 (0.190); in men, TB 1.187 (0.097), TH 0.982 (0.138) and LS 1.240 (0.190). Precision error (in g/cm^2) for Lunar DPX-L in women was 0.010 (TB), 0.028 (TH) and 0.016 (LS). Precision error using Lunar Prodigy for women was 0.009 (TB), 0.009 (TH) and 0.039 (LS). Precision error using Lunar Prodigy for men was 0.007 (TB), 0.014 (TH), and 0.031 (LS).

Mean change in aBMD (in g/cm^2) per year in women was, for TB -0.003 (0.007), for TH -0.011 (0.016) and for LS 0.004 (0.015). Corresponding results in men were -0.003 (0.006), -0.006 (0.009) and 0.005 (0.016) at TB, TH and LS respectively.

The number of individuals with 5-year aBMD change at TB that exceeded the LSC was 244 women (38.6%) and 73 men (35.6%). The corresponding results at TH were 265 women (41.4%) and 78 men (38.6%); at LS the numbers were 303 women (45.0%) and 51 men (24.6%).

Monitoring time interval (i.e. LSC/median rate of change in aBMD) for both populations was 8 years (for TH aBMD) and 13 years (for LS aBMD). Based on Prodigy precision data, the monitoring time intervals for women were 3 and 32 years for TH and LS, respectively.

Discussion

To the best of my knowledge, this study as part of the Malmö OPRA study has been the largest study in elderly women to assess the ability to predict bone loss over several years. The design of the OPRA study has several advantages: it has (i) a well-defined population, (ii) a high attendance rate, (iii) a thorough ascertainment of fracture, (iv) a long follow-up, and (v) the use of novel and established bone turnover markers. The overall aim of the work described in this study was to improve the prevention of fragility fractures in the future. There are numerous risk factors for fragility fracture. Bone mineral density is one of the most important risk factors that is potentially modifiable. For diagnostic purposes, a diagnostic threshold is used for bone density test results, below which the term osteoporosis is used. However, a large proportion of individuals who sustain a fragility fracture are not osteoporotic (4, 23, 24). Apart from the fact that they do not take other risk factors into account, bone density test results only reveal the current situation. They do not show the ongoing bone turnover; thus, they do not provide information on future changes in bone density.

There are several reasons for the development and use of bone turnover markers. The work in these studies illustrates efforts to find ways of assessing future bone loss by the measurement of bone turnover markers (**Study II and III**), of how to improve this assessment (**Study IV**), and to investigate whether some markers are more specific than others (**Study I–IV**). Since the time required to assess bone density changes with bone density equipment is very long (**Study V**), it seems unreasonable to follow up compliance and effect of anti-osteoporotic medication by repeated bone density measurements.

Currently, bone turnover markers are being used extensively in research applications and also being tested as tools for the management of metabolic bone diseases such as osteoporosis and Paget's disease in clinical practice, because these markers are non-invasive and relatively inexpensive. Monitoring of the efficacy of bone-active drugs is currently the most promising clinical application of bone turnover markers, because of the possibility of detecting a change in the levels of bone turnover markers within a few weeks of treatment (25-28). Some markers, particularly resorption markers such as S-TRACP5b, S-CTX-I, U-CTX-I, U-NTX-I and U-DPD, and some bone formation markers such as S-bone ALP and S-OC, have shown some degree of fracture predictability in different populations (10), but the prediction is not strong enough to use in individual patients. The fracture predictability afforded by bone turnover markers is weaker than the predictability afforded by DXA (29), but it is somewhat inconsistent between studies (30-34).

A high rate of bone turnover is associated with a high rate of bone loss and osteoporosis (35, 36). Early

detection of individuals who are at high risk of developing osteoporosis could be important for clinical decision-making. In particular, individuals with osteopenia and individuals with a high rate of bone loss may need more careful follow-up.

In **Study II** and **III**, baseline bone turnover markers, in particular S-OCs, U-DPD/crea, S-TRACP5b, S-CTX-I, U-LongOC/crea and U-MidOC/crea could be correlated to the rate of change of aBMD in the legs. To some degree, there were correlations with rate of change of aBMD in the arms, in the total body, in part of the body, in the total hip and in the femoral neck. None of the markers were found to be correlated to the rate of change of aBMD at the lumbar spine; nor did S-Bone ALP and U-TotalOC/crea show any correlation with rate of change of aBMD. When the correlation between bone turnover markers and 5-year change of QUS variables was examined, all markers except S-Bone ALP showed correlations with changes in SoS, while none of the markers showed any correlation with changes in BUA **(Study III)**. When the mean of serial measurement of bone turnover markers was used instead of baseline measurement, the correlations became stronger as the number of samples used increased, and the women with constantly elevated levels of bone turnover markers had a significantly higher rate of bone loss **(Study IV)**.

In general, the correlation between bone turnover markers and the change in aBMD was not strong. The strongest correlation coefficients were 0.22 when the baseline levels were used and they were 0.32 when the mean of four serial measurements was used. None of the markers proved to be superior to the others. Bone formation and resorption markers had almost similar magnitudes of correlations. This could be due to the tight coupling of bone formation and resorption. This idea is supported by the results of **Study I**, in which no difference between bone formation markers and resorption markers in TSU of ^{99m}Tc-MDP was found. Bone turnover markers are released from the whole skeleton. This may be the reason for higher correlations with bone turnover markers at large skeletal sites including the total body, the partial body and the legs, than smaller sites such as the femoral neck and the lumbar spine (**Study II and IV**).

Many other factors also affect the clinical usefulness of bone turnover markers. Pre-analytical conditions affecting bone turnover markers such as age, gender, menopausal state, ethnicity and recent fracture are not controllable, whereas other factors such as the effect of food intake, physical activity and circadian rhythm can be controlled (37). The OPRA study was designed to control factors such as age, gender, ethnicity and menstrual status. Samples were taken in the morning in the non-fasting state, which could have affected the results, mainly the S-CTX-I levels (38). Many other factors such as time of the day, recent fracture and level of physical activity may have an effect on bone turnover markers. The study design was deliberately not changed during the study period, and all samples were collected in the same manner to make comparisons possible within the cohort.

Bone density has a smaller annual change or response to anti-resorptive and anabolic treatment compared to the response of bone turnover markers. Precision has an effect on the shortest follow-up interval between repeated scans. In the population-based cohorts in **Study V**, several years were needed to detect a significant change between measurements. The estimated monitoring time intervals (i.e. least significant change / median rate of change in aBMD) were between 3 and 32 years, depending on the site of measurement and the equipment used. Only when a high degree of bone loss is expected may a shorter follow-up time be useful. Thus, DXA has shortcomings in detecting rapid losers and individuals with a high risk of developing osteoporosis.

Single measurements of bone turnover markers and follow-up measurements of DXA both have limitations in their ability to detect individuals with rapid bone loss. Serial assessments of bone turnover markers can substantially improve the ability to find individuals with increased loss of bone density. Whether or not intervals shorter than one year could be used to improve the predictive ability of bone turnover markers remains to be evaluated.

Conclusions

There is a correlation between levels of bone turnover markers and the rate of bone loss in elderly women, with varying degrees of correlation coefficients at different skeletal regions. In general, bone turnover markers correlate better with change in aBMD at large skeletal sites, such as the total body, and weight-bearing sites such as the legs, than with aBMD change at specific clinically important regions such as the femoral neck and the total hip. Correlations between bone turnover markers and rate of bone loss become stronger when serial measurements of bone turnover markers are used. The individuals with constantly high levels of bone turnover markers have higher change in aBMD. However, these correlations may not be strong enough to be predictive of bone loss at the level of the individual patient. DXA is used to monitor change in aBMD to aid in treatment decisions. However, long durations of follow-up are needed to detect aBMD changes in elderly women and men that exceed the least significant change. DXA is therefore of limited use in the longitudinal monitoring of bone loss.

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