Monitoring patients on osteoporosis therapy

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The goal of osteoporosis therapy is fracture risk reduction. Only a limited amount of fracture risk reduction can be explained by increases in bone mineral density (BMD). Reductions in fracture risk occur long before the changes in BMD. However, with antiresorptive agents, bone turnover markers decrease as early as 3 months after initiation of therapy. Studies show that a decrease in bone turnover markers is a better predictor for reduction in fracture risk than increase in BMD. Bone turnover markers can be used as an adjunct to BMD in monitoring patients with osteoporosis. Guidelines suggest that BMD measurements should be performed with central dual energy x-ray absorptiometry at least 1–2 years apart with the same instrument each time, provided that precision studies are carried out. Results should be compared with the least significant change calculated for that particular instrument. There are no guidelines regarding the use of bone turnover markers, but measuring them 3–6 months after initiation of antiresorptive therapy would be appropriate to document that they are within the reference interval for healthy premenopausal women.

Keywords: bone mineral density, bone turnover markers, fracture risk, height loss, least significant change, monitoring, osteoporosis, precision, spine radiograph, variability

future medicine part of fsg

The ultimate goal of osteoporosis therapy is the reduction in fracture risk. In clinical trials, the efficacy of treatment options is measured by comparing fracture rates among patients receiving antiresorptive agents and placebo. However, in the individual patient, a decrease in fracture rate cannot be used to monitor the effectiveness of therapy. A new fracture does not mean that the treatment is not working and absence of fracture in the short term does not mean that the treatment is effective. Bone mineral density (BMD) is used as a surrogate measure of treatment efficacy both in clinical practice and clinical trials. Many clinical trials with antiresorptive agents have shown that an increase in BMD is associated with reduction in fracture risk [1–3]. In these trials, reduction in fracture risk was achieved even when there was limited or no increase in BMD. The reduction in fracture risk correlated well with the reduction of bone turnover markers (BTM).

It is also established that monitoring changes in individual patients increases compliance to treatment [4]. However, compliance with the treatment is very poor in osteoporotic patients. This is especially true for the patients with asymptomatic disease diagnosed according to WHO criteria (i.e., T score ≤ -2.5), rather than the patients with complicated disease who have fractures. The need for long-term use to see real differences in BMD and concerns about potential side effects among patients result in the discontinuation of drugs. The response rates to therapy based on BMD changes in clinical trials range from 70 to 85%, even among highly compliant patients [5]. Once the efficacy of a drug is established by BMD and/or BTM and the patients are convinced that their treatment is effective, the compliance of the patients to the therapy will improve.

This review will summarize the monitoring of osteoporosis therapy in clinical practice, current use of BMD and BTM in monitoring, advantages and pitfalls of BMD and BTM, and provide recommendations for their use in clinical practice.

Clinical monitoring

History & physical examination

As with all aspects of clinical medicine, monitoring begins with obtaining vital signs at triage and obtaining a history and physical examination at each visit. In terms of vital signs, one should not anticipate a change in weight, pulse rate or blood pressure. Very occasionally, a patient taking medications for osteoporosis and hypothyroidism may demonstrate a slowing down of the pulse rate. The instructions for bisphosphonates state that the medication should be taken on an empty stomach with a full glass of water but no other medications or food. The instructions for taking L-thyroxine state that the medication should be taken during a period that is preferentially 2 h before or 2 h after a meal and that concomitant medication may interfere with absorption. In particular, calcium taken at the same time as L-thyroxine decreases the absorption of the latter. Patients on both drugs should be taught this initially and reminded at each visit.

The history-taking is straightforward; any potential side effects from therapy, all new medications and any new diagnoses or symptoms should be documented. The physical examination will be dictated by the history, but will be normal in most patients without fractures and without secondary causes of osteoporosis. However, height loss, back tenderness, paraspinal muscle contraction, thoracic kyphosis, lumbar lordosis or scoliosis and protruding abdomen may be detected in patients with vertebral fractures.

Fracture detection

All patients on osteoporosis therapy should have their standing height accurately measured at each visit using a wall-mounted stadiometer with the patient shoeless and the head positioned in the Frankfort plane. These stadiometers are very accurate but one must be aware that height does change during the course of the day. Several studies have attempted to determine exactly what height loss might represent a new vertebral fracture in someone who has not experienced the acute pain of a possible fracture between visits. There is no firm answer but any loss of more than 1 cm should arouse the suspicion that a fracture has occurred. Simonoski and colleagues proposed a prospective height loss of 2.0 cm over 1–3 years [6]. The negative predictive value of this threshold was 85.1%, therefore new vertebral fracture can be ruled out with an acceptable degree of accuracy. The positive predictive value was only 58.7%; therefore, a new vertebral fracture can be suggested but cannot be diagnosed by height measurement alone. Consequently, patients with height loss greater than 2.0 cm should undergo lateral spine radiographs to confirm a new fracture. Krege and colleagues suggested that the probability of a new vertebral fracture is increased fourfold with the presence of back pain, threefold with prior vertebral fracture and threefold with a height loss of 2.0 cm or greater [7]. Any information about a new fracture does not represent a treatment failure – in the definitive clinical trials there were always some patients on therapy that fractured. Additionally, finding a new asymptomatic fracture is not *per se* an immediate indication to consider a change in therapy. A radiograph might be more appropriate in those patients who have already sustained one or more fragility fractures, as multiple fractures may be a clue to change therapy from an antiresorptive agent to an anabolic agent.

Standard laboratory investigations

The drugs that are approved for the prevention of bone loss or the treatment of osteoporosis are safe and generally have no major adverse nonskeletal effects that require frequent monitoring. The major exception is estrogen or estrogen-plus-progestin therapy early in the menopause where annual mammography is indicated. There is no clear indication, for purposes of monitoring osteoporosis therapy, to a biochemical or hematology profile, or obtain any urine measurements. Teriparatide may cause transient hypercalcemia but this is usually observed only during the first 4–6 h after each injection. Occasionally, patients may develop sustained, mild hypercalcemia. It is recommended that fasting serum calcium levels should be monitored after 1 month of teriparatide therapy [8]. If hypercalcemia persists, daily dietary calcium intake should be restricted to 1000 mg at most or the dosing frequency of teriparatide should be reduced to alternate days. In other situations, there is no real indication for monitoring calcium levels outside of the annual physical examination.

Bone densitometry

Current clinical evidence and guidelines suggest monitoring BMD changes in response to therapy measured by dual energy x-ray absorptiometry (DXA) [9–12]. However, several issues regarding both technical and clinical interpretation of serial DXA results have to be addressed.

Technical aspects in the interpretation of DXA results

The rationale behind serial BMD measurements is to define what changes in BMD are clinically significant in order to identify responders and nonresponders to the therapy. A physician can easily change or discontinue the therapy because of a small increase or no change in BMD. In most cases, these changes do not exceed the least significant change (LSC). LSC is any change (increase or decrease) in BMD exceeding the precision error of the machine, which is considered to be clinically significant, rather than the measurement error of machine or technician at a given confidence interval (mostly 95%). In order to calculate LSC, DXA facilities must perform an *in vivo* precision study. Precision refers to the ability of the technique to reproduce the same results when the test is carried out repeatedly in the same manner without a real biological change. Precision of DXA then reflects the precision error of the machine and the error contributed by the technician. DXA is not

perfectly reproducible as is the case with most techniques used in clinical medicine. Therefore, performing a precision study for each skeletal site is mandatory to indicate whether it is a real biological change or not. This is done by measuring 15 patients three times or 30 patients two times, repositioning the patient each time and then calculating the standard deviation (SD) or percentage of coefficient of variation (% CV) for the group. LSC can then be calculated as 2.77 × SD (or % CV), which reflects with 95% confidence that the difference between two consecutive measurements is greater than can be accounted for by inherent 'noise' in the method [13]. Most facilities have precision errors of 1–1.5% for the spine and 1.5–2% for the hip. The precision error of the hip is greater than the spine because of variability in hip positioning. With a precision error of 1% at the spine, LSC with a 95% confidence interval is 2.8%. The time required to exceed this value is 1 year for bisphosphonates and estrogen and 2 years for raloxifene [14]. Therefore, repeating BMD after 2 years of initiation of antiresorptive therapy will be more appropriate than measuring it at 1 year, and an increase of 3–4% should be considered clinically significant. For the hip, the time interval will be longer due to smaller increases at cortical sites than trabecular sites. Even though the spine is not the best site for diagnosis of osteoporosis in the elderly (age 70 years or over), owing to the high prevalence of degenerative changes, it is the recommended site for monitoring since it is mainly composed of trabecular bone.

Another problem with DXA monitoring in controlled clinical trials is regression to the mean. In the Fracture Intervention Trial (FIT), women taking alendronate whose hip BMD decreased by more than 4% during the first year had an overall mean increase of 4.7% during the second year. By contrast, those who seemed to gain at least 8% during the first year lost an average of 1% during the next year [15]. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, women taking raloxifene whose hip BMD decreased by more than 4% during the first year had an average increase of 4% in the second year, and those who gained at least 8% during the first year lost an average of 2.8% during the next year [15]. This phenomenon is called regression to the mean, in which measurements obtained repeatedly over time tend to be closer to the mean of the population. This is not a true biological variation and physicians should not stop or change treatment on the basis of a modest bone loss during the first year.

To overcome these technical problems, repeat BMD should be performed on the same instrument as the baseline study, on which quality control and precision studies have already been done. Both physicians and patients should be informed that the expected response is a slight increase or no change in BMD.

Clinical aspects in BMD monitoring

The relationship between low or decreasing BMD and fracture risk is exponential and well established. This relationship becomes exponential at T-scores below -2.5 even though patients above this score do fracture. However, it is not clear whether an increase in BMD during treatment is related to a reduction in fracture risk and, if so, to what extent BMD increase contributes to a reduction in fracture risk. Clinical trials with bisphosphonates, raloxifene and calcitonin demonstrated similar reductions of approximately 35–50% in vertebral fracture risk despite different ranges of spine BMD increases of 1.2–8.3%, although these agents were not compared in the same study [14].

In a meta-analysis of 13 trials of antiresorptive agents including alendronate, risedronate, etidronate, tiludronate, calcitonin, raloxifene and estrogen, Wasnich and Miller found a statistically significant relationship between an increasing spine or hip BMD and a reduction in spine fracture risk [1]. They stated that 70–80% of fracture risk reduction was attributable to BMD increase. However, some authors argued that the relationship between BMD changes and reduction in fracture risk was inconsistent. In a meta-analysis of Cummings and colleagues, there was a significant relation between increasing spine BMD and reduction in vertebral fracture risk, yet only a small percentage of this reduction was attributable to a BMD increase [3]. For example, only 16% of risk reduction was attributable to BMD increases in the FIT trial. For raloxifene, only 4% of the reduction in vertebral fracture risk was related to BMD increases [16], and for risedronate this number was up to 28% [17]. The inconsistency of the relationship between BMD changes and fracture risk reduction can be explained by the presence of other risk factors and predictors of bone strength. These are muscle strength, risk of fall, age, skeletal geometry, bone microarchitecture and bone turnover. The results of these meta-analysis showed that a small reduction in vertebral fracture risk could be anticipated even if there is no change in

BMD. Therefore, patients who maintain their BMD on therapy should not be regarded as treatment failures. However, patients who have significant decreases in BMD (greater than the LSC) should be evaluated for compliance, intercurrent illnesses and secondary causes of osteoporosis.

BMD can also be used to assess the patient's compliance to the therapy. However, current evidence does not suggest that serial BMD measurements increase the compliance. Since osteoporosis is usually an asymptomatic disease and BMD changes occur slowly over time, patients have to wait for 2 years for their first follow-up BMD. However, most patients tend to discontinue their medication before their first follow-up BMD. In the FIT trial, 76% of patients who were noncompliant to treatment discontinued alendronate during the first year [18]. Therefore, more research is needed to introduce practical and alternative tests for monitoring osteoporosis therapy.

Bone turnover markers

Bone turnover is a coupled process of bone resorption and bone formation. Bone loss occurs when the balance between resorption and formation shifts towards the former. Bone turnover is reflected in serum or urine by the measurement of BTM (**Box 1**). BTM cannot be used to diagnose and predict bone mass but may be useful for predicting fracture risk [19], especially in the elderly, predicting future bone loss (fast losers vs slow losers), selecting patients for therapy and monitoring response to therapy. Monitoring response to therapy is the most commonly established use of BTM in clinical practice. However, problems in analytical and biological variability and absence of formal guidelines for daily practice limit their routine use by many physicians.

Box 1. Currently available serum and urine bone turnover markers.

Bone formation markers:

- Serum
  - Bone alkaline phosphatase
  - Osteocalcin
  - Carboxyterminal extension peptide of procollagen Type I
  - Aminoterminal extension peptide of procollagen Type I

Bone resorption markers:

- Serum
  - Tartrate-resistant acid phosphatase
  - N-telopeptide of Type I collagen
  - C-telopeptide of Type I collagen
- Urine
  - Hydroxyproline
  - Pyridinoline
  - Deoxypyridinoline
  - N-telopeptide of Type I collagen
  - C-telopeptide of Type I collagen

Variability in BTMs

Analytical variability of BTM has been solved for the most part by recently available serum tests and the introduction of automated analyzers [20]. However, there are still some uncontrollable factors besides controllable factors. Uncontrollable factors include age, gender, ethnicity, muscle mass, menopausal status and some disease states such as renal failure, drugs, recent fractures and immobility. There is also an effect of food intake on these markers and circadian variation. These factors should be taken into account when interpreting the results, and reference ranges for each marker should be established for the individual laboratory. Controllable factors include circadian and seasonal variability and diet. Most BTMs increase at night, reaching a peak between 2 and 8 am and then decrease rapidly reaching a nadir between 1 and 11 pm [21]. Circadian variability is greater for resorption markers than for formation markers; however, the diurnal variation in individual patients is substantially less than the effect of therapy on the markers. Ideally, the samples should be collected at the same time of day for serial studies, preferably as an early morning fasting sample. In clinical practice this is impractical since it requires an additional visit for the patient and the impact on clinical care in an individual patient is minimal given the marked inhibitory effect of therapy on these markers. Calcium supplementation taken at night, bisphosphonate treatment and fasting suppress circadian variability of BTM. Serum and urine levels of most BTMs are otherwise unaffected by diet, except for hydroxyproline, a marker of bone resorption. Seasonal variability is not a universal finding, although most studies suggest increased levels of most BTMs during winter, except for bone alkaline phosphatase, which is decreased [21]. Seasonal changes may be of importance when monitoring short-term responses to therapy. To reduce the effect of circadian variability and to increase the reproducibility of serial measurements, serum and urine samples must be collected in the morning after an overnight fast before 9 am. Urine samples must be

either first or second morning void with creatinine correction. Changes in markers should also be compared with the LSC. The literature cites the LSC as 45–65% for most resorption markers and 25% for most formation markers, but there are some problems with these assessments.

Effects of osteoporosis therapy on bone turnover markers

In published clinical trials, there is a dose-dependent decrease of 50% or more in resorption markers within 3 months of the initiation of antiresorptive therapy [22–24]. These levels remain low as long as the effective therapy is continued. The nadir in formation markers is not reached before 6 months. Bisphosphonates and estrogen induce the greatest changes in BTM, whereas raloxifene and calcitonin induce smaller changes [21]. With bisphosphonate therapies that have a long half-life in the skeleton, BTM will remain low for many months after therapy has been discontinued. This is shown for alendronate but may not be the case for risedronate, in which an immediate increase in bone resorption markers was shown after discontinuation of therapy [17]. With calcitonin, estrogen and raloxifene that are not incorporated into the skeleton, the effect on BTM dissipates very rapidly once therapy is discontinued. In the case of teriparatide, one would expect an early increase of formation markers. The response of resorption markers to teriparatide has been reported to be variable. Most of them were increased except urine hydroxyproline, pyridinoline and deoxypyridinoline, which were decreased in one study [25]. Some data suggest a disproportionate increase in resorption and formation markers. However, in most trials, the increase in formation markers is greater and occurs earlier than the increase in resorption markers. These increases in BTM were shown to be transient, returning to normal when treatment is discontinued [26].

Prediction of BMD changes & fracture risk reduction by BTMs during treatment

Although baseline BTM measurement does not appear to be a useful parameter in predicting future BMD responses under treatment, changes in BTM during treatment (either as an absolute value or a percentage of initial value) are strongly associated with a long-term increase in BMD. Several studies of estrogen and bisphosphonates have shown that short-term (3–6 month) decreases in BTM correlate well with long-term (1–2 years) increases in BMD [21]. An early treatment decrease in BTM means that the follow-up BMD will be increased or unchanged from the baseline BMD, and this will in turn increase the compliance to treatment. An early treatment increase in BTM should prompt a physician to assess compliance or underlying diseases. For teriparatide, increases in C-terminal extension peptide of procollagen Type I at 1 month and amino-terminal extension peptide of procollagen Type I at 3 months correlated best with increases in spine BMD at 18 months [27].

In most clinical trials of osteoporosis treatments, changes in BTM levels have been shown to be better predictors of fracture risk reduction than changes in BMD [17,28–30]. With risedronate, a 60% reduction in urine N-telopeptide of Type I collagen and 51% reduction in C-telopeptide of Type I collagen at 3–6 months were associated with a reduction in vertebral fracture risk (75% in 1 year and 50% in 3 years). Similar reductions were found in nonvertebral fracture risk [17]. The relationship between a reduction in vertebral fracture risk and changes in BTM were not linear, suggesting a level of bone resorption below which no further reduction in fracture risk occurs. In the FIT study, alendronate-treated women with at least a 30% reduction in bone alkaline phosphatase had a lower risk of vertebral and nonvertebral fractures [28].

BMD response to osteoporosis treatment can be slow and variable, especially in the case of raloxifene [14]. Despite a small 2–3% increase in BMD, fracture risk reduction may be up to 50%. In the MORE trial, only 4% of the reduction in vertebral fracture risk was related to BMD increases [16]. In another analysis of the MORE trial, percentage change in osteocalcin was able to predict reduction in vertebral fracture better than the percentage change in BMD [29]. Recent meta-analyses are in concordance with individual trials that demonstrate changes in BTM during treatment predict fracture risk reduction better than BMD changes [1–3]. With most antiresorptive agents, reductions in fracture risk occur within 1 year of treatment, long before the increases in BMD occur. In these meta-analyses, small reductions in fracture risk in the absence of significant BMD changes were attributed to early changes in bone turnover.

Recommendations for monitoring osteoporosis therapy in daily practice

Regular physician visits and height measurement during these visits are essential to detect new vertebral fractures. Current osteoporosis

guidelines accept BMD measurement by central DXA as the surrogate measure for monitoring osteoporosis therapy [9–12]. Although peripheral techniques, such as quantitative ultrasonography, single energy x-ray absorptiometry, radiographic absorptiometry, peripheral DXA and peripheral quantitative computed tomography (pQCT) can be used for the prediction of fracture risk [31], and diagnosis of osteoporosis in rare and exceptional situations when central DXA is not available, they are not recommended for patient monitoring.

The North American Menopause Society (NAMS), American Association of Clinical Endocrinologists (AACE) and International Society for Clinical Densitometry (ISCD) suggest both the hip and spine for monitoring therapy [10–12]. Since changes over time occur more rapidly in trabecular bone than in cortical bone and the spine is mostly composed of trabecular bone, it may be reasonable to monitor changes with spine BMD. However, for women aged 60 years or above, the hip may be the preferred site because a high prevalence of degenerative changes in the spine makes the interpretations unreliable [10].

According to the NAMS follow-up BMD should not be repeated before 2 years in women receiving therapy and before 3–5 years in untreated women [10]. According to the ISCD, BMD should be performed annually until therapeutic effect is established and then at longer intervals [12]. The AACE also recommends annual BMD until therapeutic effect is established and thereafter at 2-year intervals [11]. The AACE also suggests a follow-up BMD in 3–5 years for untreated women. These intervals are recommended according to precision studies and LSC. LSC is generally reached in 1 year in the spine and 2 years in the hip. Follow-up BMD must be performed on the same instrument. Only in certain situations in which rapid bone loss is anticipated BMD should be performed at more frequent intervals. In patients receiving glucocorticoids, BMD should be performed every 6 months.

No formal guidelines regarding the use of BTM exist. It is recommended to maintain BTM levels within the reference interval (preferably in the lower half) for healthy premenopausal women. There are no data to support the use of BTM in the selection of a specific therapy. Therefore, it is not necessary to obtain a pretreatment level. However, most physicians feel comfortable having a baseline value and most patients are interested to see a change on therapy. There are also no data to support the superiority of one marker over another. It is best to monitor antiesorptive agents with resorption markers and anabolic agents with formation markers. Resorption markers should be checked 3 or 6 months after initiation of therapy and formation markers should be checked after 6 months. If the levels are not within the desirable range, a repeat test should be carried out 4–6 weeks before considering noncompliance, intercurrent illnesses or secondary causes of osteoporosis. Once BTM reaches a low point in therapy, it will remain low as long as the patient is compliant. Therefore, it is not necessary to monitor BTM regularly.

Conclusion

BMD measurements have long been used for the management of osteoporosis. Besides being the gold standard for the diagnosis of osteoporosis, BMD is a strong predictor of fracture. An increase in BMD under treatment is strongly associated with a reduction in fracture risk. Therefore, BMD measurement by DXA is accepted as crucial in monitoring osteoporosis therapy, provided that there is quality control for DXA machines. Although greater increases in BMD are associated with greater reductions in fracture risk, a small increase or no change on therapy is also related to a reduction in fracture risk, indicating that reductions in fracture risk occur long before increases in BMD. Therefore, other factors such as bone turnover play a role in fracture risk reduction. BTM are useful for predicting the risk of fracture. Studies have shown that changes in BTM during treatment are better predictors of fracture risk reduction than changes in BMD. Combining the use of BMD and BTM may improve fracture risk reduction and may increase compliance to treatment. The guidelines suggested by several authorities are in agreement about how to use BMD in clinical practice, but guidelines regarding the use of BTM are lacking due to variability in these markers. The authors of this article strongly encourage physicians to use BTM in monitoring treatment effectiveness as an adjunct to BMD.

Early monitoring after the initiation of therapy should be after approximately 3–4 months and include history, physical examination and a measurement of a BTM. Additional monitoring is only needed at the time of the patient's annual physical examination, although some patients will want to have reassurance more often. Follow-up DXA should be performed after 2 years of therapy. Provided that is satisfactory, additional follow-up should simply be the 2-yearly DXA.

Executive summary

Introduction

- The goal of osteoporosis treatment is a reduction in fracture risk.
- Both bone mineral density (BMD) and bone turnover markers (BTMs) predict fracture.
- Changes in BMD and BTMs during treatment are related to a reduction in fracture risk.
- Compliance to therapy in osteoporosis is low and monitoring can increase compliance.

Clinical monitoring

- History and physical examination should be obtained at each visit.
- Height loss of more than 2 cm over 1–3 years predicts a new vertebral fracture and should prompt a physician to order lateral spine radiographs.

Bone densitometry

- Quality control and precision studies for dual energy x-ray absorptiometry (DXA) devices should be performed at each facility.
- Least significant change (LSC) must be calculated using precision errors. This then identifies the time interval for serial DXA scans.
- The relationship between increasing BMD and reduction in fracture risk is demonstrated in clinical trials but the extent of this relationship is unclear.
- A small reduction in fracture risk can be anticipated even if there is no change in BMD.
- Other factors, such as bone turnover and microarchitecture, may contribute to a reduction in fracture risk.
- There is no evidence to suggest that monitoring patients with BMD increases compliance.

Bone turnover markers

- Monitoring response to therapy is the most commonly established use of BTM in clinical practice.
- Analytical and biological variability and absence of formal guidelines for daily practice limit their routine use by many physicians.
- There is a dose-dependent decrease of 50% or more in resorption markers within 3 months of initiation of antiresorptive therapy, but the nadir in formation markers is not reached before 6 months.
- Changes in BTM during treatment are strongly associated with a long-term increase in BMD.
- Changes in BTM levels have been shown to be better predictors of fracture risk reduction than changes in BMD.

Recommendations for monitoring osteoporosis therapy in daily practice

- Central DXA should be used to monitor changes in BMD. Peripheral devices are not recommended for this purpose.
- The spine is the preferred site for monitoring but the hip can also be used.
- Serial BMD measurements should be carried out with at least 2-year intervals to exceed LSC, but some guidelines suggest 1 year until stability has been established.
- No guidelines exist regarding the use of BTMs.
- BTMs should be checked 3–6 months after initiation of therapy.
- It is recommended that BTM levels are maintained within the reference interval (preferably in the lower half) for healthy premenopausal women.

Conclusion

- BMD and BTMs must be used together in monitoring osteoporosis therapy.

Future perspective

- Gender- and ethnic-specific databases for BMD and BTM measurements are needed for men and non-White women.
- There is a need to assess the use of peripheral BMD devices for the management of osteoporosis.
- Techniques should be improved to overcome variability in BTM measurements and reference ranges should be identified more precisely.
- Use of both BMD and BTMs to increase compliance should be investigated.
- Use of peripheral quantitative computed tomography and virtual bone biopsy should be investigated by further trials to assess microarchitectural changes and their use in clinical practice.

Future perspective

Although BMD and BTM are useful for monitoring osteoporosis therapy, there are several limitations that need to be overcome. Most available data came from studies performed on White postmenopausal women. Gender- and ethnic-specific databases for BMD measurements are needed for men, premenopausal women and non-White populations. This will improve diagnosis, fracture risk assessment and hence monitoring in these populations. There is also a need for assessing the use of peripheral BMD measurements in the global management of osteoporosis, since they are smaller, less expensive and more portable than central DXA devices.

Several issues have to be solved for BTM. More studies should be carried out to improve analytical variability, to define normal ranges in response to

therapy and to identify which marker or combination of markers should be used for a given therapy. Also, normal values should be established for men and non-White women. Prospective studies for both BMD and BTM are needed to evaluate if these measures can be used to increase compliance to treatment. Furthermore, introduction of teriparatide to clinical practice increased the need for new prospective studies in which all of the issues mentioned above should be investigated for monitoring patients on anabolic therapy.

BMD and BTM partially explain the reduction in fracture risk. They do not give information about microarchitectural changes of bone. pQCT and high-resolution magnetic resonance imaging (termed virtual bone biopsy [VBB]) have been developed for the assessment of microarchitecture at distal radius and distal tibia and have the potential to assess fracture risk. A recent study in hypogonadal men demonstrated that men receiving testosterone have preservation of microarchitecture but men on placebo have deterioration [32]. Available data suggest that microarchitectural changes can be seen earlier than the changes in DXA and a smaller number of patients are needed to conduct serial studies. Therefore, we can assume that both pQCT and VBB are promising tools for the diagnosis of osteoporosis, fracture risk assessment and monitoring osteoporosis therapy. However, more clinical and technical research has to be carried out on pQCT and VBB before becoming clinically applicable.

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