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# Monitoring of osteoporosis therapy



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Over the past two decades, major advances have been made in the number and range of agents available for the treatment of osteoporosis, all with proven anti-fracture efficacy. Unfortunately, compliance with these treatments is not optimal, and a number of patients could be considered as non-responders. Consequently, monitoring anti-osteoporotic therapy could be part of successful osteoporosis management. Currently, no formal well-accepted clinical practice guidelines are available for monitoring anti-osteoporosis therapies. Changes in bone mineral density and bone turnover markers, while on therapy, have potential value in monitoring treatment but their assessment and, consequently, their benefits could be limited by metrological and clinical issues. Moreover, their effectiveness is probably drug dependant. Recommendation for the standardisation of the methodology when analysing the potential relevance of tools for the monitoring of osteoporosis therapy is needed.

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## Introduction

Osteoporosis is a major health problem worldwide. It is defined as a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk. Technological developments for the measurement of bone mineral density (BMD) have led to diagnostic criteria that are widely applied. The World Health Organization diagnostic criterion for osteoporosis is a BMD measurement equal to or more than 2.5 standard deviations below the young female reference mean (T-score  $\leq -2.5$  standard deviation) [1]. In addition,

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there have been major advances in the number and range of agents available for treatment, all with proven anti-fracture efficacy [2]. These agents have differing modes of action in protecting against fracture, and this needs to be taken into account when developing monitoring strategies. Important gaps in the clinical management of osteoporosis include the identification of individuals who would best benefit from intervention and, for those on treatment, the optimal manner in which response to treatment should be monitored.

The goal of pharmacological therapy is to reduce fracture risk by increasing bone strength. The ideal method of evaluating success with drug therapy would be to compare pre-treatment fracture risk with post-treatment fracture risk, or directly to measure changes in bone strength. For individual patients in clinical practice, we must rely on surrogate markers (biomarkers) that are correlated with bone strength and fracture risk. A working group of the National Institutes of Health defined biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention,” with applications that include “use for prediction and monitoring of clinical response to an intervention” [3]. It has been proposed that an acceptable biomarker for osteoporosis therapy should meet established standards for accuracy, precision, and reliability, with well-defined quality control procedures, standardized data acquisition, and methods for analysis, and show (a) biological plausibility, (b) a significant association between the biomarker and fracture in the target non treated population, (c) consistent biomarker changes in response to treatment, and (d) that changes in biomarker predict the fracture reduction on treatment [4]. Moreover, another requirement is that if the biomarker indicates a lack of response, appropriate changes in management can be made by the health care prescriber and, in the case of poor adherence to treatment, patient behaviour can be modified [5]. At last, in a world with limited health-care resources, monitoring should also be cost-effective [5].

Even though anti-osteoporosis treatment can be associated with a decrease in the incidence of vertebral and non-vertebral fractures, development of a new fracture does not necessarily represent failure of therapy. Indeed, at best, pharmacological agents reduce fracture rates by 30–70% [2]. Therefore, an efficient monitoring of osteoporosis therapy could help to determine the effectiveness of a treatment strategy and guide management decisions.

### **Tools to monitor osteoporosis therapy**

The most widely used tools to monitor osteoporosis therapy in clinical practice are Dual X-ray Absorptiometry (DXA) and Bone Turnover Markers (BTMs). Consequently, the next sections will present a critical review of the evidence supporting the use of BMD and BTMs to monitor treatment effect as well as their clinical applications. However, it should be acknowledged that other tools have been developed to assess properties of bone [6,7]. Quantitative ultrasound measures the speed of sound and broadband ultrasound attenuation at peripheral skeletal sites, but there is no clear evidence that these parameters are clinically useful in monitoring therapy. Quantitative Computed Tomography (QCT) and peripheral QCT measure volumetric BMD in trabecular and cortical bone, but could hardly be recommended as a monitoring tool in clinical practice because it is more expensive, less widely available, and exposes the patient to a higher dose of ionizing radiation than DXA. Finite element analysis has not been validated as an outcome measure in clinical trials and cannot be recommended as a monitoring tool. At last, high resolution magnetic resonance imaging and high resolution peripheral QCT at peripheral skeletal sites measure trabecular microarchitecture but are not validated tools to measure treatment effect.

### **BMD by DXA**

Several national and international guidelines, including the International Society for Clinical Densitometry (ISCD), recommend BMD measurements for the routine monitoring of treatment. In particular, the ISCD states [8] that (a) Serial BMD testing can monitor response to therapy by finding an increase or stability of bone density; (b) Serial BMD testing can evaluate individuals for non-response by finding loss of bone density, suggesting the need for re-evaluation of treatment and evaluation for secondary causes of osteoporosis; (c) Follow-up BMD testing should be done when the expected

change in BMD equals or exceeds the least significant change (LSC); (d) Intervals between BMD testing should be determined according to each patient's clinical status: typically one year after initiation or change of therapy is appropriate, with longer intervals once therapeutic effect is established. These statements reemphasize the fact that the use of BMD measurement as a tool to monitor osteoporosis treatment raises both metrological and clinical issues.

### *Metrological issues*

Accurate detection of BMD changes during treatment requires that the change is greater than the precision error of the measurement. Reproducibility is far better for BMD measurement than for most laboratory tests. Reproducibility is usually 1–2% at the spine and 2–3% at the hip. However, these data obtained under highly controlled conditions may not apply to everyday clinical practice. Many factors could affect the accuracy of BMD testing, including inter-machine variance as well as the experience of the operator. Therefore, any repeat DXA scan should ideally be performed with the same machine [9]. Because all testing methods have variations in successive measurements due to random fluctuations, a statistically significant change in BMD must exceed the expected test-to-test variation. In clinical practice, the method most widely used to categorise changes in BMD during therapy is to estimate the LSC, derived from the standard deviation of the precision error of the measurement. With a confidence interval of 95%, the LSC is calculated as  $2.77 \times CV$  (Coefficient of variation). When serial measurements are obtained in a patient, only changes greater than the LSC can be ascribed to treatment effects [8,10]. Smaller changes may be related to measurement error.

The utility of BMD testing to monitor therapy was questioned almost a decade ago when the concept of “regression to the mean” was raised [11]. Regression toward the mean is a statistical phenomenon in which values obtained over time tend to move closer to the mean, as compared to initial values. For instance, within a patient population, those individuals with the largest BMD gains after 1 year will tend to have the smallest gains after 2 years, and vice versa. However, the use of the LSC shows that these individual variations are related to fluctuations in measurement error rather than to genuine biological variations [12]. Consequently, although this concept has relevance at a population level, it was subsequently refuted as misleading and irrelevant to the clinical management of individual patients [13,14].

### *Clinical issues*

Although increases in BMD resulting from various pharmacological treatments differ widely, reported reductions in vertebral fracture risk are rather similar [2]. Studies exploring the association between BMD changes and fracture reduction have been mainly conducted with antiresorptive agents. However, they provide contradictory results [15–22] that are mainly dependant on the drug used. Anyway, even if some associations have been observed between an increase in BMD and a reduced fracture risk [2,14,15], the relationship is probably not linear. Indeed, fracture risk decreases soon after the beginning of the therapy and can precede a measurable improvement in BMD [23,24]. Some studies have shown that fracture risk can decrease with no change in BMD [25] and even despite a slight decrease in BMD [26,27].

The predictive value of BMD changes for fracture risk reduction is still debated for antiresorptive agents and, at this time, there is limited evidence that BMD is a reliable indicator of fracture risk reduction with antiresorptive agents. Data suggest however that the correlation between changes in BMD and fracture incidence could be stronger with other agents [28–30]. For example, we have shown a strong association between changes in total hip or femoral neck BMD, but not spine BMD, and vertebral fracture incidence in patients treated with strontium ranelate [28,30]. For each 1% increase in femoral neck BMD, the relative risk of new vertebral fracture decreased by 3% (1%–5%) and for each 0.010 g/cm<sup>2</sup> increase in femoral neck BMD, the risk to experiencing a new vertebral fracture was reduced by 6% (3%–10%).

All these results suggest that the interest in assessing BMD changes as a way of monitoring osteoporosis therapy could be drug dependant. However, it should be acknowledged that the cost-effectiveness of monitoring osteoporosis treatment using repeated BMD measurements has not been formally assessed.

## BTMs

In contrast to BMD, which typically changes in response to therapy less than 2–5% per year, or a maximum of 3% in 3–6 months, most of osteoporosis therapies act by reducing or increasing individual BTM levels or their ratios by 30–200% within 3–6 months [31]. However, as for BMD, the use of BTM measurement as a tool for monitoring osteoporosis treatment raises both metrological and clinical issues.

### *Metrological issues*

The use of biochemical markers for monitoring osteoporosis therapy in clinical practice is limited by their pre-analytical and analytical variability [32]. Pre-analytical variability is particularly important and includes both modifiable factors (e.g. time of day (i.e. circadian variability), fasting status and exercise) and non-modifiable factors (e.g. age, sex, menopausal status, fractures, pregnancy, lactation, immobility, co-morbidities such as thyroid disease, diabetes mellitus, impaired renal function, liver disease, and drugs such as glucocorticoids, anticonvulsants, heparin, gonadotropin hormone releasing agonists) [33]. Analytical variability is effected by processing of the specimen (e.g. collection, handling, and storage). The impact of pre-analytical and analytical variability may be different according to both the type of BTM and type of assay used. It is important to note that the absence of uniform standardisation still is a concern and makes it difficult to compare values obtained by different methods in different laboratories [34]. This is why all measurements for one individual should be done in the same laboratory.

As for BMD, at the individual level, in order to be confident that a change in a BTM value has actually occurred, the change in measured value must exceed the LSC (i.e.  $2.77 \times CV$ ). One method to reduce the LSC and, consequently, to improve confidence is to undertake several baseline estimates and to use the mean value but this is impracticable in everyday clinical practice. However, in clinical practice, a one sided rather than two-sided probability of 0.05 is appropriate since the direction of change is known and the LSC would be  $2.33 \times CV$  [35].

### *Clinical issues*

Changes in BTMs with treatment are associated with changes in BMD, both for antiresorptive therapy [36] and for anabolic therapy [37]. A systematic review published in 2011 and limited to postmenopausal osteoporosis and marketed therapies, analysed the correlations between short-term BTM changes and fracture risk reduction or BMD variation [38]. The authors showed that most of the studies found correlations between serum BTM and BMD changes under antiresorptive therapies, although inconsistently between drugs. However, as previously discussed the changes in BMD with therapy are not closely related to the fracture risk reduction, particularly with antiresorptive therapy.

Several studies have described the relationship between the reduction in BTMs following antiresorptive therapy and the reduction in vertebral and non-vertebral fracture risk [35]. These studies showed in general that the larger the decrease in BTM, the larger the reduction in fracture risk. The 2011 systematic review also assessed the associations between short-term BTM changes and fracture risk reduction [38]. It was shown that there was more evidence for the prediction of fracture risk reduction with bone formation serum BTM including PINP than with serum CTX but with high heterogeneity between trials. Another review also showed inconsistency between the changes in BTM and fracture risk reduction with different treatments [35]. At least, short term changes in BTM only explain part of the fracture risk reduction observed with anti-osteoporotic treatment.

Indeed, the percent of treatment effect explained was only calculated for few studies, and ranged from 0 to 77% [22,39–41]. Once again, this could be dependent on the treatment but also on the BTM used.

All individual studies analysed in these reviews have some limitations. Few have used the LSC value cut-off. Sometimes, only part of the study population had a BTM assessment and ways to improve pre-analytical variability was not optimal (e.g. non-fasting sampling or first morning urine).

As BMD with DXA, BTMs have potential value in monitoring treatment even if they could be drug dependant. Anyway, more studies are required before clear clinical practice recommendations can be made.

## Discussion

Some elements deserve further discussion:

- Impact of the monitoring on compliance with the treatment. Poor compliance and little persistence with osteoporosis treatments are common and associated with reduced anti-fracture efficacy [42]. Indeed, most patients discontinue anti-osteoporosis medications after a few months because of administration constraints, side effects, or lack of interest. Even if BMD cannot reliably predict treatment response within an appropriate time frame, it could be argued that regular measurements provide reassurance and improve motivation to persist with treatment. However, there is no evidence that BMD monitoring improves adherence to therapy. Using BTM, some studies, but not all, have suggested that repeated measurements of some BTMs could slightly improve adherence or persistence to treatment but this statement has to be further investigated [43–46].
- Clinical trial data vs real world data. Patients in clinical trials are different from patients treated in the “real world.” In an original study, it was shown that, in the best case scenario, 80% of patients being treated in their practice would have been excluded from participation in one of the trials, whereas in the worst case scenario, 97% would have been excluded from another [47].
- Monitoring as an incentive to begin a discussion between patient and physician. It has been hypothesized that a significant decrease in BMD or too small changes in BTM would alert the physician to assess issues that could influence the treatment of osteoporosis (e.g. compliance with treatment, secondary causes of osteoporosis) [48]. However, it is argued that most physicians can address these issues without using medical resources or repeating DXA [49].
- Non-responder patients. In patients who apparently fail to respond to treatment [50], there is no evidence that other therapies could be successful.

## Summary

Monitoring anti-osteoporotic therapy, with the objective to detect non-compliant or non-responder patients, is part of a successful osteoporosis management. Currently, there are no formal well-accepted clinical practice guidelines for the monitoring of anti-osteoporosis therapies. In epidemiological or clinical studies of patients receiving a treatment against their osteoporosis, changes in BMD or BTM have generally been associated with a decreased fracture risk but this effect is largely drug dependant. In clinical practice, their use for the monitoring of osteoporosis therapy could be limited by metrological and clinical issues. More researches must be performed before clear practical recommendations for the monitoring of anti-osteoporosis medication can be made.

### Practice points

- Monitoring the efficacy associated with anti-osteoporotic drugs is part of a successful osteoporosis management
- Monitoring may help to identify poor-compliant patients or non-responder patients
- Formal well-accepted clinical practice guidelines for the monitoring of anti-osteoporosis therapies do not exist
- Bone mineral density and bone turnover markers have potential value in monitoring treatment but their effectiveness are probably drug dependant

### Research agenda

- Alternative approaches to bone mineral density and bone turnover markers in the monitoring of anti-osteoporotic therapy need be investigated.
- From a health-economics point of view, restricting monitoring to the high-risk population of poor compliance or non-response should be investigated. However, these high-risk populations should first be identified.
- Since variability of the bone turnover markers is a substantial limitation in their use in clinical practice, every ways to decrease the variability (i.e. use of new techniques, better standardisation, development of new markers) could have an impact.
- Recommendation for the standardisation of the methodology when analysing the potential benefits of tools for the monitoring of osteoporosis therapy do not exist and would be more than welcome.

### References

- [1] Kanis JA, McCloskey EV, Johansson H, et al. A reference standard for the description of osteoporosis. *Bone* 2008;42:467–75.
- \*[2] Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2013;24:23–57.
- [3] Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89–95.
- [4] Bouxsein ML, Delmas PD. Considerations for development of surrogate endpoints for antifracture efficacy of new treatments in osteoporosis: a perspective. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2008;23:1155–67.
- [5] Compston J. Monitoring osteoporosis treatment. *Best practice & research. Clin Rheumatol* 2009;23:781–8.
- [6] Lewiecki EM. Monitoring pharmacological therapy for osteoporosis. *Rev Endocr Metabolic Disord* 2010;11:261–73.
- [7] Baum T, Karampinos DC, Liebl H, et al. High-resolution bone imaging for osteoporosis diagnostics and therapy monitoring using clinical MDCT and MRI. *Curr Med Chem* 2013;20:4844–52.
- [8] Baim S, Wilson CR, Lewiecki EM, et al. Precision assessment and radiation safety for dual-energy X-ray absorptiometry: position paper of the International Society for Clinical Densitometry. *J Clin Densitom Official J Int Soc Clin Densitom* 2005;8:371–8.
- [9] Koita S, Ravaud P, Fechtenbaum J, et al. Follow-up of individual patients on two DXA scanners of the same manufacturer. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2000;11:709–13.
- \*[10] Roux C, Garnero P, Thomas T, et al. Recommendations for monitoring antiresorptive therapies in postmenopausal osteoporosis. *Jt Bone Spine Rev Du rhum* 2005;72:26–31.
- [11] Cummings SR, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. *Fracture Intervention Trial Research Group. JAMA J Am Med Assoc* 2000;283:1318–21.
- \*[12] Ravaud P, Reny JL, Giraudeau B, et al. Individual smallest detectable difference in bone mineral density measurements. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 1999;14:1449–56.
- [13] Bonnick SL. Monitoring osteoporosis therapy with bone densitometry: a vital tool or regression toward mediocrity? *J Clin Endocrinol Metabolism* 2000;85:3493–5.
- [14] Lenchik L, Watts NB. Regression to the mean: what does it mean? Using bone density results to monitor treatment of osteoporosis. *J Clin Densitom Official J Int Soc Clin Densitom* 2001;4:1–4.
- [15] Cummings SR, Karpf DB, Harris F, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 2002;112:281–9.
- [16] Sarkar S, Mitlak BH, Wong M, et al. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2002;17:1–10.
- [17] Hochberg MC, Greenspan S, Wasnich RD, et al. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metabolism* 2002;87:1586–92.
- [18] Delmas PD, Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. *Bone* 2004;34:599–604.
- [19] Delmas PD, Li Z, Cooper C. Relationship between changes in bone mineral density and fracture risk reduction with antiresorptive drugs: some issues with meta-analyses. *J Bone mineral Res Official J Am Soc Bone Mineral Res* 2004;19:330–7.
- [20] Austin M, Yang YC, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2012;27:687–93.
- [21] Detilleux J, Reginster JY, Chines A, et al. A Bayesian path analysis to estimate causal effects of bazedoxifene acetate on incidence of vertebral fractures, either directly or through non-linear changes in bone mass density. *Stat Methods Med Res* 2012. <http://dx.doi.org/10.1177/0962280212456655>. [Published online].

- [22] Bruyere O, Detilleux J, Chines A, et al. Relationships between changes in bone mineral density or bone turnover markers and vertebral fracture incidence in patients treated with bazedoxifene. *Calcif Tissue Int* 2012;91:244–9.
- [23] Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA J Am Med Assoc* 1999;282:1344–52.
- [24] Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2000;11:83–91.
- [25] Chapurlat RD, Palermo L, Ramsay P, et al. Risk of fracture among women who lose bone density during treatment with alendronate. The fracture intervention trial. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2005;16:842–8.
- [26] Watts NB, Cooper C, Lindsay R, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. *J Clin Densitom Official J Int Soc Clin Densitom* 2004;7:255–61.
- [27] Watts NB, Geusens P, Barton IP, et al. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2005;20:2097–104.
- [28] Bruyere O, Roux C, Detilleux J, et al. Relationship between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. *J Clin Endocrinol Metabolism* 2007;92:3076–81.
- [29] Chen P, Miller PD, Delmas PD, et al. Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2006;21:1785–90.
- [30] Bruyere O, Roux C, Badurski J, et al. Relationship between change in femoral neck bone mineral density and hip fracture incidence during treatment with strontium ranelate. *Curr Med Res Opin* 2007;23:3041–5.
- \*[31] Reginster JY, Collette J, Neuprez A, et al. Role of biochemical markers of bone turnover as prognostic indicator of successful osteoporosis therapy. *Bone* 2008;42:832–6.
- [32] Seibel MJ. Biochemical markers of bone turnover: part I: biochemistry and variability. *Clin Biochem Rev/Aust Assoc Clin Biochem* 2005;26:97–122.
- [33] Hannon R, Eastell R. Preanalytical variability of biochemical markers of bone turnover. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2000;11(Suppl. 6):S30–44.
- \*[34] Bergmann P, Body JJ, Boonen S, et al. Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. *Int J Clin Pract* 2009;63:19–26.
- \*[35] Vasikaran S, Eastell R, Bruyere O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2011;22:391–420.
- [36] Greenspan SL, Resnick NM, Parker RA. Early changes in biochemical markers of bone turnover are associated with long-term changes in bone mineral density in elderly women on alendronate, hormone replacement therapy, or combination therapy: a three-year, double-blind, placebo-controlled, randomized clinical trial. *J Clin Endocrinol Metabolism* 2005;90:2762–7.
- [37] Chen P, Satterwhite JH, Licata AA, et al. Early changes in biochemical markers of bone formation predict BMD response to teriparatide in postmenopausal women with osteoporosis. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2005;20:962–70.
- \*[38] Funck-Brentano T, Biver E, Chopin F, et al. Clinical utility of serum bone turnover markers in postmenopausal osteoporosis therapy monitoring: a systematic review. *Seminars Arthritis Rheumatism* 2011;41:157–69.
- [39] Eastell R, Barton I, Hannon RA, et al. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2003;18:1051–6.
- [40] Reginster JY, Sarkar S, Zegels B, et al. Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. *Bone* 2004;34:344–51.
- [41] Sarkar S, Reginster JY, Crans GG, et al. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. *J Bone Mineral Res Official J Am Soc Bone Mineral Res* 2004;19:394–401.
- [42] Rabenda V, Mertens R, Fabri V, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2008;19:811–8.
- \*[43] Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metabolism* 2004;89:1117–23.
- [44] Delmas PD, Vrijens B, Eastell R, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metabolism* 2007;92:1296–304.
- \*[45] Silverman SL, Nasser K, Nattrass S, et al. Impact of bone turnover markers and/or educational information on persistence to oral bisphosphonate therapy: a community setting-based trial. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2012;23:1069–74.
- [46] Roux C, Giraudeau B, Rouanet S, et al. Monitoring of bone turnover markers does not improve persistence with ibandronate treatment. *Jt Bone Spine Rev Du rhum* 2012;79:389–92.
- [47] Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2000;11:533–6.
- [48] Rothman MS, Miller PD, Lewiecki EM, et al. Bone density testing: science, the Media, and patient care. *Curr Osteoporos Reports* 2014;12:227–9.
- [49] Muncie Jr HL, LeBlanc LL. Monitoring osteoporosis treatment: DXA should not be routinely repeated. *Am Fam Physician* 2010;82:749–54.
- \*[50] Diez-Perez A, Adachi JD, Agnusdei D, et al. Treatment failure in osteoporosis. *Osteoporos Int J Established as Result Coop between Eur Found Osteoporos Natl Osteoporos Found USA* 2012;23:2769–74.