REVIEW ARTICLE

The use of biochemical markers of bone turnover in osteoporosis

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Objective: **Present evidence-based recommendations on the use of biochemical markers of bone turnover in the management of osteoporosis.**

Methods: **The English literature from 1999 to 2005 was reviewed by using data sources from MEDLINE.**

Results: **Measurement of biochemical markers of bone turnover helps us identify a high bone turnover rate. Elevated levels of these markers points towards a pathology and at an accelerated loss of bone mass. Its main utility is in documenting the response to therapy. They have a limited role in the follow-up of patients with osteoporosis. To be useful, bone markers must be measured at baseline and periodically after the beginning of therapy. A fall of on fifty (50%) percent in the levels of resorption markers between the third and sixth month of therapy predicts a good response. Bone markers can not be used to establish the diagnosis of osteoporosis. Neither do they measure bone mass. Markers are not capable of predicting future loss of bone mass in an individual nor do they correlate with the occurrence of previous fractures. The greatest limitation of these measurements is not being able to measure bone remodeling in the individual subject. Bone resorption markers are more frequently used than those of formation. The levels of the markers can identify the failures to the therapy and responses to therapy. Lack of reduction in the resorption markers could indicate lack of compliance with therapy, problems of absorption of the medication or lack in response to treatment. There may be problems with the measurement and the interpretation of results of bone remodeling markers. Variability between individuals and intra-individual variability exist as well as inter-assay and intra-assay variability.**

Conclusion: **Biochemical markers of bone turnover along with measurements of bone density can help optimize the management of osteoporosis. The use of the bone markers is not recommended in a routine form, but they can be of utility in situations of poor compliance with the therapy or when there are difficulties in the management of the treatment of osteoporosis.**

Key words: Osteoporosis, Bone markers, Bone remodeling.

Biochemical markers of bone turnover are substances that serve as indicators of bone remodeling activity, either bone destruction or formation. Measurement in bone markers has a role in the diagnosis and treatment of osteoporosis.

Bone is a living tissue which is constantly changing by bone remodeling, a normal physiological mechanism by means of which old bone is replaced by new bone. This process occurs in sequential stages beginning by the activation of the osteoclasts, cells that undermine the bone forming a groove or resorption pit. Osteoblasts deposit a collagen substance called osteoid in these pits. Osteoid is mineralized, the pit is closed and the old bone is replaced by new bone. Bone remodeling process occurs at different sites and speed. During this process, components of the bony matrix, substances and enzymes are released. The release of these substances reflects the dynamics of bone remodeling. The released substances are known as the biochemical markers of bone remodeling.

Osteoclasts are originated of the lineage of the hematopoyetic cells, have an average of life of three weeks and are the cells in charge of bone resorption. Osteoblasts are the osteoid-producing cells. Osteoblasts originate of mesenchymal cells and have an average half-life of three months. Osteoblasts transforms into osteocytes, their membrane contains high amounts of alkaline phosphatase.

Bone remodeling is a constant process and in adult humans the bone is replaced totally every ten years. During stages of growth and around menopause this process is accelerated. Bone remodeling and its markers thus vary during different stages in life. High levels of bone markers during puberty are a manifestation of the normal physiological process of the growth spur.

Bone mineral density (BMD) is a static measurement of bone mineralization. BMD is the measurement that is used to define osteoporosis, since loss of bone density is linked to bone fragility and susceptibility to fractures. BMD is also used to monitor response to osteoporosis therapy.

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The measurement of the bone markers could be of aid in the evaluation and management of osteoporosis and other metabolic diseases of bone. Their measurement could also contribute to the prediction of bone fractures. The level of the markers gives an idea of the magnitude of bone formation and destruction and could help in therapeutic decisions.

During the past few years several substances have been described that give us an idea of bone remodeling. These tests are not-invasive, of a relatively high cost and that can be obtained rather easily. Its role in the handling of the osteoporosis is still being defined. Bone markers depicting bone formation may be measured in serum or urine. The markers of bone destruction or resorption are all products of degradation of collagen and can also be measured in urine or in serum. Bone resorption markers have been studied more extensively than bone formation markers.

Biochemical Markers of Bone Formation

Collagen is osteoblasts' main product, but is not exclusive of the bone. The measurement of the pro-peptides of Type I collagen carboxy-terminal (PICP) or amino terminal (PINP) helps to determine bone formation although it has its limitations. The biological markers of bone formation are not specific for bone formation (1). These substances do not distinguish between the normal and pathological process of bone formation. The concentrations of osteocalcin (OC), PINP, PICP and bone-specific alkaline phosphatase (BALP) in serum correlate with the rate of bone formation. Alkaline phosphatase (ALP) is an enzymatic protein present in cellular membranes. ALP is secreted by the liver, kidneys, spleen, intestine and some tumors, in addition to the bone. ALP has an average life of one to two days. Upon measuring the bone fraction of the ALP, the BALP, the specificity improves. The measurement of the OC also has its limitations. OC is a polypeptide that is incorporated in the bone matrix and it is freed to the circulation during bone resorption. Serum levels of OC indicate bone resorption as much as bone formation. OC serum levels vary during the day, with a circadian rhythm. Levels of OC and BALP do not correlate in a direct form. Substances such as PINP, PICP and ALP are also secreted with a pattern of circadian rhythm, with levels which vary throughout the day (highest) and night (lowest).

In general, the higher the level of biological markers of bone formation, the greater is the remodeling process. Patients with high bone turnover are at a greater risk to undergo bone fractures. High levels biological markers of bone formation can be used to identify the subjects that are increasing their bone mass. Bone formation markers are depicted in Table 1

Table 1. Biochemical Markers of bone formation Abbreviation

Alkaline Phosphatase	ALP
Bone Specific Alkaline Phosphatase	BSAP
Osteocalcin	OC
Propeptide of Type I Collagen Carboxy-terminal	PICP
Propeptide of Type I Collagen Amino-terminal	PINP

Biochemical Markers of Bone Resorption

Bone resorption is increased around the menopause and in periods of fracture repair. It is also increased in hyper-parathyroidism, hypercortisolism and with glucocorticoid use.

The biological markers of destruction or bone resorption represent degradation of collagen products. Traditionally hydroxyproline (OHP) has been the measure of bone resorption, but the use of this marker is limited by its lack of specificity to bone collagen. The measurement of this test is affected by foods and is difficult to perform. The test TRAP, tartrate-resistant acid phosphatase, has been a deception. TRAP is secreted by osteoclasts, but is not specific to them.

The pyridinolines cross-links of collagen (NTX or CTX) are amino acids coming from collagen and excreted without degradation. This it is the best studied assay for bone resorption. The cost of measuring NTX or CTX has been decreasing. They are all affordable. The pyridinolines work as bridges in the collagen and are broken during the bone resorption process. NTX and CTX are degraded in the liver and the kidneys and converted to deoxypyridinoline, Dpd. They are measured in serum or urine. The results of the tests of these biological markers have their problems: variability between different assays exists, variation with the time of taking the sample, variation with food ingestion and the results vary by gender and age. The preferred measurement the biological markers of pyridinolines are in twenty-four (24) hours urine collections. Dpd is the bone marker of choice for bone resorption. There is not a good correlation between the levels of biological markers of bone resorption in serum and urine. If serum is used, the sample has to be drawn before nine in the morning. Bone resorption markers are depicted in Table 2

Possible Uses of the Biochemical Markers of Bone Turnover

Traditionally, bone densitometry is measured by dual X-ray absorptiometry (DXA). To document a significant

Table 2. Biochemical Markers of bone resorption

	Abbreviation
Tartrate-resistant acid Phosphatase	TRAP
Hydroxyproline	OHP
Pyridinolines-total and free	pYD
Deoxypyridinolines-total and free	dPD
Cross-linked C-Telopeptide	CTX
Cross-linked N-Telopeptide	NTX

change in the bone mass by this method a waiting period of one to two years is needed. The measurement of biological markers have their utility in shortening this period, but they should only be measured if that information is going to impact the treatment of the patient (2). The biological markers help to predict an increase in bone density, without having to wait a year to see the response (3). The measurement of the bone markers can more quickly document the response to therapy. They are able to identify the bone that has a slow bone remodeling against a fast one. Anti-resorptive medications cause a reduction of the levels of biological markers. This reduction occurs between two to six months after beginning the therapy. First the biological markers of bone resorption are reduced and soon after, the biological markers of bone formation are reduced. The degree on reduction depends on the potency of the anti-resorptive agent and can vary from twenty to a seventy percent (20% to 70%)

Possible Uses of Biochemical Markers of Bone Turnover

1. **Prediction of risk of bone fractures**
   The EPIDOS study showed that an increase in urinary CTX was associated to an increase in the risk of hip fractures in post-menopausal women [OR=2.2 (CI 95% 1.3-3.6)] (4). The OFELY study also demonstrated an increase in the risk of hip fractures in post-menopausal women associated to an increase in CTX, with a OR of 2 (95% 1.2-3.8) (5).
2. **Document Response to therapy of osteoporosis.**
   Pierre Delmas and collaborators (6) showed that it is possible to use the measurement of biochemical markers of bone turnover to predict long term mineral density in post-menopausal women who used hormonal replacement therapy. In the VERT (7) study an association was demonstrated between the levels of bone resorption markers measured between three and six months after the beginning of therapy with bi-phosphonates and vertebral fractures three years later. Several clinical studies have demonstrated that short term reduction of bone remodeling markers is translated in a statistically significant increase in the bone mineral density in the spine and radius (in one to two years) A reduction of a sixty-five percent (65%) of NTX , fifty-five percent (55%) of CTX and forty percent (40%) of OC can predict an increase of BMD of a three percent (3%) after two years of therapy with alendronate (8).
3. **Individualize osteoporosis therapy**
   There are people with active remodeling and others whose bones are inactive. One theorizes that the therapy with anabolic agents would be of greater benefit in this last group, whereas those of high remodeling rate would have greater benefit with the anti-resorptive therapies. Clinical data have not confirmed this theory.
4. **Document bone remodeling**
   Bone biopsy with histo-morphometry is the best method of documenting bone remodeling, but this is an invasive and painful procedure. Bone remodeling can be documented in a non-invasive and less painful form by means of taking blood or urine samples. Biochemical markers of bone turnover change quickly after beginning therapy. Treatment with oral bi-phosphonates induces a reduction in bone remodeling.

Alendronate produces a reduction of seventy percent (70%) in CTX, beginning the second month of therapy and reaching a plateau at the third month. Reduction of bone markers of bone formation begin at the sixth month. This effect in the markers is maintained during long periods of treatment, for up to ten years. Upon discontinuing the therapy, the levels of the markers slowly rise, but they remain below the pre-treatment levels.

Risedronate induces a reduction of sixty percent (60%) in resorption markers, which rise immediately upon discontinuing the therapy.

Hormonal replacement therapy induces a reduction in resorption markers that reach a plateau three to six (3-6) months later. Upon discontinuing the hormonal therapy, markers rise to pre-treatment levels.

Raloxifene produces a reduction in bone resorption with a drop of thirty to forty percent (30-40%) in bone resorption markers and twenty to thirty percent (20-30%) in formation markers.

Teriparatide, an anabolic agent, causes an increase in OC, a marker of bone formation, of fifty –five percent (55%) and of CTX, bone resorption marker, of a twenty percent (20%). These increases are observed after two months of the beginning of the therapy.

Glucocorticoids therapy causes an accelerated bony resorption and a deceleration of bone formation. This is translated in a diminution of OC (9) and an elevation of bone resorption markers.

Advantages of Measuring Bone Turnover Markers

1. Identify fast bone losers
2. Determine response to therapy in weeks
3. Document compliance with therapy

Disadvantages of Use of Markers of Bone Turnover

Methods of measuring biochemical markers of bone turnover vary. Results of the biochemical measurement vary with physical activity, with the circadian rhythm and the seasons of the year. This disadvantage has been reduced when using methods of automated immuno-tests.

1. Lack of consensus of which constitutes a high versus a low risk group of developing bone fractures. Fractures can occur even in slow remodeling bones.
2. There is a weak association between measures of BMD and levels of bone remodeling markers.
3. Cost of the measurement of the markers can be a limiting factor in its use.
4. There is variability of the measures of bone resorption markers in individuals according to age, menopause status, presence of fractures and skeletal size.
5. Inability to establish cumulative bone loss.
6. Can not be used to predict loss of bone mass.

Conclusions and Recommendations on the Use of Biochemical Markers of Bone Turnover

The use of biochemical markers of bone turnover can help in the management of osteoporosis. Its main utility is in documenting the response to therapy. Bone markers must be measured at baseline and periodically after the beginning of the therapy. A fall of on fifty (50%) percent in the levels of resorption markers between the third and sixth month of therapy predicts a good response (10). Biochemical markers of bone turnover can not be used to establish the diagnosis of osteoporosis. They do not measure the bone mass either. Measurement of the biochemical markers of bone turnover helps us identify a high turnover rate. High levels of these markers points towards a pathology and at an accelerated loss of bone mass. Measurement of bone markers in a patient with osteopenia showing a high turnover rate could help in the decision making of starting therapy. Nevertheless, the markers are not capable of predicting future loss of bone mass in an individual nor do they correlate with the occurrence of previous fractures.

The biochemical markers of bone turnover have a limited role in the follow-up of patients with osteoporosis. Although in clinical studies, a reduction of the level of the bony markers predicts an increase in bone mineral density, the limitations in its individual application are multiple. One of the limitations of the use of bone resorption markers is that they do not measure bone remodeling in the individual (11). They are a good measure of remodeling in populations studies. Bone resorption markers are used more frequently than those of formation. The levels of the markers can identify the failures to the therapy and responses to therapy. Lack of reduction in the resorption markers could indicate lack of compliance with therapy, problems of absorption of the medication or lack in response to treatment.

There may be problems with the measurement and the interpretation of results of biochemical markers of bone turnover. Variability between individuals and intra-individual variability exist as well as inter-assay and intra-assay variability. A consensus does not exist on as to the optimal value of bone markers. Dr. Paul Miller, based on opinions, in guides developed in 1999 suggests that pre-menopausal bone markers levels indicate effectiveness of the therapy. Guides on the use of bone remodeling markers do not exist as of today (12-13). Use of these markers, along with the measures of bone density, aid in the best management of osteoporosis. The use of the bone markers is not recommended in a routine form. Nevertheless, they can be of much utility in situations of poor compliance with the therapy or when there are difficulties in the management of the treatment of osteoporosis.

Resumen

Objetivo: Hacer recomendaciones sobre el uso de los marcadores de recambio óseo en el manejo de la osteoporosis basadas en evidencia científica. *Métodos:* Se revisó la literatura médica en inglés que aparece en MEDLINE de los años 1999 al 2005. *Resultados:* Los marcadores de recambio óseo ayudan a identificar el hueso que tiene una tasa alta de recambio. Elevaciones en dichos marcadores se asocian a patología y a una pérdida acelerada de masa ósea. Su utilidad principal es documentar la respuesta a terapia. Los marcadores tienen un papel limitado en el seguimiento de los pacientes con osteoporosis. Los mismos deben medirse al comienzo del tratamiento y luego periódicamente. Si se documenta una reducción de los marcadores de resorción ósea de un cincuenta por ciento (50%), se puede predecir una respuesta adecuada al tratamiento. Los marcadores no miden la masa ósea ni sirven para establecer el diagnóstico de osteoporosis. Tampoco son capaces de predecir en

individuos futura pérdida de masa ósea o correlacionan con fracturas previas. Su limitación mayor es que no miden el proceso de remodelación ósea en el individuo. Los marcadores de resorción se utilizan más que los de formación. La medición de los marcadores puede ser de ayuda en identificar respuesta a terapia. Documentar ausencia de disminución en los marcadores es indicativo de falla en la terapia para osteoporosis, problemas de absorción de los medicamentos o falta de respuesta a los mismos. Hay problemas con la medición de los marcadores y la interpretación de los resultados, así como variabilidad entre los ensayos. *Conclusión:* El uso de estos marcadores, junto con las medidas de densidad ósea, ayuda al mejor manejo de la osteoporosis. Al presente no se recomienda el uso de los marcadores de recambio óseo en una forma rutinaria. Sin embargo, pueden ser de mucha utilidad en situaciones de pobre cumplimiento con la terapia o cuando hay dificultades en el manejo del tratamiento de la osteoporosis.

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