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ORIGINAL ARTICLE

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Correlation of different bone markers with bone density in patients with rheumatic diseases on glucocorticoid therapy

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Abstract Osteoporosis is a common concomitant disease in patients with rheumatic diseases on glucocorticoid (GC) therapy. Bone status is usually evaluated by determination of bone density in combination with clinical examinations and laboratory tests. However, the strength of individual biochemical bone makers in GC-induced osteoporosis has yet to be fully clarified. For this reason, different bone markers were investigated in correlation with bone density in patients with rheumatic diseases. Approximately 238 patients (212 women, 26 men) with a rheumatic disease and under GC therapy were examined consecutively for the first time with regard to bone density (BMD) and bone markers {osteocalcin, bone-specific alkaline phosphatase (precipitation method/tandem-MP ostase), crosslinks [pyridinoline (PYD), deoxypyridinoline (DPX), N-terminal telopeptide (NTX)]}. The daily glucocorticoid dose was 10 mg prednisone equivalent (median), and the cumulative dose was 12 g prednisone equivalent (median). None of the patients had previously taken medication for osteoporosis. Osteoporosis was demonstrated in 35.3% of the patients, osteopenia in 47.5%, and a normal BMD in 17.2%. The results of tandem-MP ostase correlated with the BMD of the lumbar spine and of the femoral neck. The values for N-terminal telopeptide and pyridinoline correlated only with the bone density of the femoral neck. All results were statistically significant, although the correlation coefficients were low. After classification of the patients according to their BMD values (osteoporosis, osteopenia and normal BMD), there were significantly more patients with bone markers above the norm in the osteoporosis group and in the osteopenia group than in the group with normal bone density. All bone markers recorded behaved similarly in relation to the bone density values. The same analysis was also undertaken for the different disease groups. In these subgroups there was also a correlation between ostase/crosslinks with BMD, but the correlation coefficients were low. A general recommendation for the routine use of a specific bone marker in patients with rheumatic diseases on glucocorticoid therapy cannot be made from a cost-benefit point of view mainly because of limited predictive power (low correlation coefficients, incomplete correlation with different sites of BMD measurement).

Keywords Glucocorticoid-induced osteoporosis · Bone markers · Rheumatic diseases

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Introduction

Osteoporosis is a common and serious concomitant phenomenon of glucocorticoid therapy [1]. Causally, apart from the direct cell-mediated effects on osteoblasts, osteoclasts and osteocytes, the effects on parathormone, vitamin D metabolism, renal function, sex-hormone secretion and the gastrointestinal tract play a major pathogenetic role. Glucocorticoids modify the proliferative and metabolic activity of bone cells. This results in inhibition of osteoblastogenesis and a shortening of the life and limitation of the function of these cells. In addition, glucocorticoids possibly cause stimulation of osteoclasts. The summation of these glucocorticoid effects results in reduction of bone generation and a lesser influence on bone resorption, which ultimately leads to osteoporosis [1].

The importance of confirming the diagnosis and starting treatment at an early stage has been described

repeatedly [2, 3]. In addition to the measurement of bone density (BMD), various different laboratory tests are applied before and during the administration of osteoporosis therapy in order to estimate the activity of bone metabolism [4]. Various biochemical markers {bone formation parameters: bone-specific alkaline phosphatase (different detection methods) and osteocalcin (OC), and bone resorption parameters: crosslinks [pyridinoline (PYD), deoxypyridinoline (DPX), and N-terminal telopeptide (NTX), etc.]} are currently being applied. The clinical benefit of OC in metabolic bone diseases was described many years ago. OC is held to be important as something of a "late" marker [5]. Bone-specific alkaline phosphatase is a further bone formation parameter. Among the various different detection methods for bone-specific phosphatase (tandem test/precipitation method), differences in specificity and sensitivity have been reported [6]. Crosslinks in the second morning urine and in 24-h urine are measured as bone resorption parameters. Apart from fluctuations according to the time of day they are also dependent on renal function [7, 8]. In earlier investigations it was possible to demonstrate that different bone markers can play a role in predicting further bone loss, sometimes even a possible fracture, in patients with postmenopausal osteoporosis. Thus, markedly higher bone losses were observed in patients with elevated NTX values than in patients with normal resorption markers. In general, an increased risk of fracture is observed when resorption markers are increased and BMD is reduced [9].

For glucocorticoid-induced (GC-induced) osteoporosis, it is not known which parameters best correlate with BMD and, therefore, should be used in daily routine for patients with rheumatic diseases. The present paper is dedicated to this question.

Materials and methods

Approximately 238 patients (212 women, 26 men) with a median age of 60.5 years (minimum/maximum 19/84 years) with various rheumatic diseases were investigated consecutively. About 81 patients had rheumatoid arthritis (RA). All patients fulfilled the classification criteria of the American College of Rheumatology (ACR) revised in 1987. Systemic lupus erythematosus (SLE) was confirmed in 40 patients according to the ACR criteria of 1982. Approximately 14 patients had a spondylarthropathy according to the classification criteria of the European Spondylarthropathy Study Group of 1991. In all patients with spondylarthropathies an X-ray of the spine was performed to exclude patients with bony outgrowths at the spine, which would lead to a false increase of BMD. A further 27 patients were suffering from vasculitis (polymyalgia rheumatica, Wegener's syndrome, panarteritis nodosa), and 76 patients were suffering from "other rheumatic diseases" (dermatomyositis, undifferentiated connective tissue disease, Sjögren's syndrome, mixed connective tissue disease, progressive scleroderma).

The median daily GC dose was 10 mg prednisone equivalent (minimum/maximum 2/75 mg), and the median cumulative GC dose was 12 g prednisone equivalent (minimum/maximum 0.2/131.4 g). The therapy lasted a median of 4 years (minimum/maximum 0.12/34 years). None of the patients had previously taken any medication for osteoporosis, including calcium and vitamin D.

The following data were collected: (a) two different bone formation markers and (b) three different bone resorption parameters. Blood was taken in the morning, and crosslinks were determined in the second morning urine.

(a) *OC* is a protein produced by osteoblasts and consists of 49 amino acids. It is incorporated into the bone matrix and is therefore a suitable marker for osteoblast function. The detected serum levels correlate with the rate of bone formation. The detection method used was chemiluminescence immunoassay. Two monoclonal antibodies with high affinity and specificity to intact OC were utilised. We used a commercial test (Human OC/Nichols Institute Diagnostics, Calif., USA).

Bone-specific alkaline phosphatase is a tetrameric glycoprotein that is found on the surface of osteoblasts and is released during osteoneogenesis. The following two test methods were applied for the determination of bone-specific alkaline phosphatase:

- Tandem-MP ostase (Beckman Coulter, Fla., USA) is an immunoradiometric method in which two monoclonal antibodies are used in a patented procedure to determine bone-specific alkaline phosphatase.
- The so-called lectin precipitation method has been established for many years. Total alkaline phosphatase is first determined here. Bone-specific alkaline phosphatase is then precipitated out by the addition of a precipitating reagent (lectin from wheat germ). Alkaline phosphatase is again determined in the supernatant. The value for bone-specific alkaline phosphatase (AP) is thus determined by evaluation of the difference.

(b) *Deoxypyridinoline*, *pyridinoline* and *N-terminal telopeptide* are fragments of the crosslinks of collagen molecules of the bone. These crosslink types are relatively specific for bone collagen, whereby PYD also occurs in cartilage. They are detected in urine samples by an ELISA technique (Osteomark, Wash., USA; Pyrilinks-TM-II-ELISA, Metra Biosystem, Germany).

In addition to the above-mentioned parameters, the values for calcium, phosphate, parathormone and vitamin D were determined for all patients, by routine laboratory tests.

BMD was measured by dual X-ray adsorption (DXA) using a LUNAR device on the left femoral neck and the lumbar spine in each patient and was stated in

grammes per centimetre squared and as a *T*-score. Osteopenia is defined as a *T*-score of less than −1 and osteoporosis by a *T*-score of less than −2.5.

Statistics

Statistical evaluation (regression analysis/correlation analysis) was conducted with the commercial statistics program SPSS. Correlation analyses according to Spearman and multivariant regression analysis were applied. The Mann–Whitney *U* test and the Wilcoxon test were used.

Results

After evaluation of the available data, osteoporosis (hip and/or spine) was confirmed in 84 patients (35.3%), osteopenia in 113 patients (47.5%), and normal BMD values in 41 patients (17.2%).

The median daily GC dose was 10 mg prednisone equivalent (minimum/maximum 5/50 mg) in the patient group with normal BMD values, 10 mg prednisone equivalent (minimum/maximum 2/75 mg) in the osteopenia group and 10 mg prednisone equivalent (minimum/maximum 2/50 mg) in the osteoporosis group. The median cumulative GC dose was 10.85 g prednisone equivalent (minimum/maximum 0.28/46.71 g) in the group with a normal BMD, 13.25 g prednisone equivalent (minimum/maximum 0.22/131.4 g) in the osteopenia group and 10.95 g prednisone equivalent (minimum/maximum 0.21/109.5 g) in the osteoporosis group. There were no statistically significant differences between the groups with regard to the daily and cumulative GC dosages.

There were also no significant differences among the groups with regard to gender. Median age was 52 years in the group with normal BMD values, 58 years in the osteopenia group and 63.5 years in the osteoporosis group. Age was significantly higher in the osteoporosis group than in the other groups ($P < 0.05$).

The same analyses with similar results were performed for the disease subpopulations (RA, SLE, spondylarthropathies, vasculitis and "other rheumatic diseases"). As a difference we found that the median age and the number of patients with osteoporosis were significantly higher in RA patients than in the other groups (Table 1).

With regard to the whole group of 238 patients, we found a negative correlation of the BMD of the femoral neck and of the lumbar spine, respectively, with the values for tandem-MP ostase (Fig. 1, Table 2). There was also a negative correlation between the BMD of the femoral neck and the bone resorption parameters NTX and PYD. All results were statistically significant, although the correlation coefficients were low (Fig. 1, Table 2). For DPX, only a trend was seen in this respect ($P = 0.08$) (Table 2). Further statistically significant correlations could not be found between BMD and the bone markers determined (Table 2). However, the two bone formation parameters and the three resorption parameters that we had recorded behaved similarly in relation to each other.

After classification of the patients into three groups according to their BMD values (osteoporosis, osteopenia and normal BMD), we found significant differences with regard to the number of patients with bone markers above the normal range. A significantly higher percentage of patients in the osteoporosis group had values above the normal range for NTX, PYD, DPX and tandem-MP ostase than the group of patients with normal BMD ($P < 0.05$) (Fig. 2). Significant differences could also be demonstrated between the patients with osteopenia and those with a normal BMD for tandem-MP ostase, NTX and DPX values ($P < 0.05$) (Fig. 2).

A further analysis was initiated to find out whether there is a correlation between BMD and the bone markers examined in the various patient subgroups (RA, SLE, spondylarthropathies, vasculitis and "other rheumatic diseases"). Also in these subgroups we detected a significant correlation between BMD and tandem AP and BMD and crosslinks. However, the correlation coefficients were always low (Tables 3, 4, 5). The corresponding data for the analyses in the vasculitis group and the group of patients with "other rheumatic diseases" were similar (not shown).

With regard to other risk factors for osteoporosis, we found a significant correlation between age and BMD of the femoral neck in the groups of SLE and RA patients ($P < 0.05$), but the correlation coefficients were low.

For the other laboratory parameters of bone metabolism recorded (calcium, phosphate, parathormone and

Table 1 Distribution of patients and presentation of results according to diagnostic categories

Parameter	All patients	RA	SLE	Vasculitis	Spondylarthropathy	Others
Number of patients (*n*)	238	81	40	27	14	76
Daily dose of GC (mg)	10	10	10	20	11	10
Cumulative dose (g)	12	8.8	20.4	7.3	12.6	12.7
Duration of treatment (years)	4	4	6	1	2.5	4
Median age (years)	60.5	65	45.5	66	51.5	58
Patients with osteoporosis; *n* (%)	84 (35.9)	41 (50.6)	12 (30)	9 (33.3)	3 (21.4)	20 (26.3)
Patients with osteopenia; *n* (%)	113 (47.5)	32 39.8)	23 (57.5)	9 (33.3)	6 (42.85)	40 (52.6)
Patients with normal BMD; *n* (%)	41 (17.2)	8 (9.8)	5 (12.5)	9 (33.3)	5 (35.7)	16 (21)

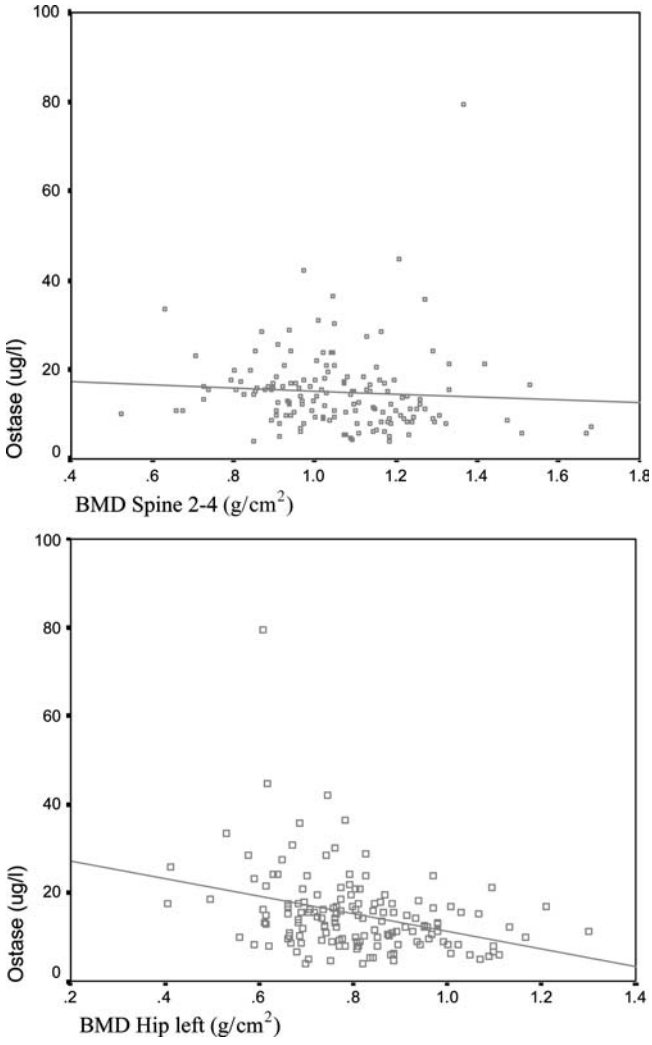

Fig. 1 Correlation of tandem-MP ostase with the BMD values of the lumbar spine ($r = -0.236$, $P < 0.05$) and the left femoral neck ($r = -0.338$, $P < 0.05$). *Left* BMD lumbar vertebrae 2–4 (g/cm^2); *right* BMD femoral neck left (g/cm^2)

vitamin D) no correlations with BMD could be demonstrated.

Discussion

Over the past few years many new laboratory tests have been introduced into osteoporosis diagnostics for assessing bone metabolism. These biochemical markers have provided a better insight into the pathological changes that occur in bone metabolism disorders and are helpful in obtaining more information regarding the personal osteoporosis risk profile of a patient. However, over the course of this rapid development, many of the high expectations placed on these markers could not be fulfilled, and the evaluation of bone markers—reflecting a dynamic process of bone formation or bone degradation—cannot precisely predict BMD, which represents the result of these processes over a prolonged period.

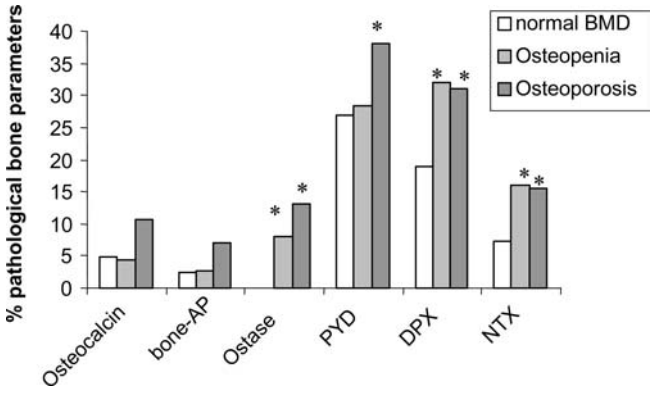

Fig. 2 Numbers of patients with normal BMD, osteopenic and osteoporotic BMD values, showing elevated bone metabolism parameter (percentage of pathological bone parameters in patients with normal BMD, osteopenia and osteoporosis) *Significantly higher than in the patients with normal BMD and elevated bone markers ($P < 0.005$)

Bone density measurement (by DXA) remains one of the best methods for confirming the diagnosis of osteoporosis today. The *T*-score values obtained by this method can be used to define osteoporosis according to the World Health Organisation (WHO) [7, 10, 11]. The results of many prospective and retrospective studies on the assessment of laboratory tests for chemical markers in postmenopausal osteoporosis have shown that, alongside BMD values, these parameters are powerful predictors of fractures, despite their high pre-analytical variability (bone-specific AP 3%, OC 4%, DPX 4%, NTX 10%) [4, 12]. This primarily applies to the resorption markers. In general, the resorption markers are considered to be early and sensitive bone markers [8, 13]. However, the predictive power of PYD is reduced in the case of rheumatic diseases accompanied by arthritis. The reason for this is that this crosslink also occurs in cartilage tissue, thus

Table 2 Correlation of bone markers with BMD values (*LV* lumbar vertebrae, *FN* femoral neck, *n.s.* not significant)

Bone marker	LV 2–4		FN left	
	Correlation coefficient	Significance	Correlation coefficient	Significance
Tandem-MP ostase	−0.236	$p < 0.05$	−0.338	$P < 0.05$
Bone alkaline phosphatase	−0.105	n.s.	−0.091	n.s.
Osteocalcin	−0.01	n.s.	−0.073	n.s.
Pyridinoline	−0.063	n.s.	−0.19	$P < 0.05$
Deoxypyridinoline	−0.025	n.s.	−0.126	n.s. $P = 0.08$
N-terminal telopeptide	−0.036	n.s.	−0.19	$P < 0.05$

Table 3 Correlation of bone markers with BMD values in the RA group (*LV* lumbar vertebrae, *FN* femoral neck, *n.s.* not significant)

Bone marker	LV 2–4		FN left	
	Correlation coefficient	Significance	Correlation coefficient	Significance
Tandem-MP ostase	0.352	$P < 0.05$	−0.177	n.s.
Bone alkaline phosphatase	0.181	n.s.	−0.053	n.s.
Osteocalcin	0.097	n.s.	−0.022	n.s.
Pyridinoline	0.180	n.s.	0.089	n.s.
Deoxypyridinoline	0.940	n.s.	−0.055	n.s.
N-terminal telopeptide	0.202	n.s.	−0.044	n.s.

Table 4 Correlation of bone markers with BMD values in the SLE group (*LV* lumbar vertebrae, *FN* femoral neck, *n.s.* not significant)

Bone marker	LV 2–4		FN left	
	Correlation coefficient	Significance	Correlation coefficient	Significance
Tandem-MP ostase	−0.425	$P < 0.05$	−0.386	$P < 0.05$
Bone alkaline phosphatase	−0.330	$P < 0.05$	−0.317	n.s.
Osteocalcin	−0.141	n.s.	−0.186	n.s.
Pyridinoline	0.197	n.s.	0.069	n.s.
Deoxypyridinoline	−0.113	n.s.	−0.105	n.s.
N-terminal telopeptide	−0.215	n.s.	−0.199	n.s.

Table 5 Correlation of bone markers with BMD values in the spondylarthropathy group (*LV* lumbar vertebrae, *FN* femoral neck, *n.s.* not significant)

Bone marker	LV 2–4		FN left	
	Correlation coefficient	Significance	Correlation coefficient	Significance
Tandem-MP ostase	−0.620	n.s.	−0.774	n.s.
Bone alkaline phosphatase	−0.243	n.s.	−0.394	n.s.
Osteocalcin	−0.293	n.s.	−0.439	n.s.
Pyridinoline	−0.425	n.s.	−0.537	n.s.
Deoxypyridinoline	−0.239	n.s.	−0.516	n.s.
N-terminal telopeptide	−0.228	n.s.	−0.531	n.s.

leading to elevated values in the case of arthritic cartilage destruction. The value of this parameter for estimating bone metabolism is, therefore, limited under such conditions. This means that it is recommendable not to use PYD as the sole marker for evaluating bone metabolism in inflammatory joint diseases [13, 14].

For patients with rheumatic diseases under GC therapy, our results show that the bone markers bone-specific AP (measured by the tandem-MP ostase test), NTX and PYD correlate with the results of BMD. However, a critical aspect to be mentioned is the fact that the correlation coefficients are very low in each case. Only a trend without significance could be demonstrated for DPX. These results correspond to our finding of a significantly higher proportion of patients with bone metabolism values above the norm (tandem-MP ostase, PYD, NTX, DPX) in the group of patients with osteoporosis than in the group with normal BMD values. For tandem-MP ostase, NTX and DPX, additional significant differences could be demonstrated between the patients of the osteopenia group and the group with normal BMD. In this regard it should be stressed that no patients in the group with normal BMD values had an elevated value for tandem-MP ostase.

The results described and discussed so far refer to the whole group of patients suffering from a rheumatic disease and being treated with GCs. However, different rheumatic diseases are known to show different patterns of bone involvement, which could limit the robustness of these data. Therefore, in order to examine the impact of the different diseases in our study, we performed subgroup analyses for patients suffering from RA, SLE, spondylarthropathies and "other rheumatic diseases". We found the data of these subgroup analyses to be in line with the data for the whole group. Therefore, we conclude that the GC therapy per se dominated the effect on the outcome parameters we measured, whereas the disease under treatment itself (apart from RA, where the number of patients with osteoporosis, and also the median age, were higher than in the other groups) is obviously secondary in this regard. A similar statement applies to the consideration of classical risk factors such as daily and cumulative GC dose or gender, since we found a significant negative correlation only between age and BMD in the whole group and in the subgroups.

We conclude from these results that the determination of tandem-MP ostase, NTX and PYD is helpful in confirming the diagnosis of GC-induced osteoporosis.

However, a general recommendation for their routine application cannot be made from a cost-benefit point of view because of the limited predictive power. In particular, the low correlation coefficients and only incomplete correlation of these parameters with different sites of BMD measurement lead to this conclusion.

Apart from this main conclusion, there are still two other issues to be discussed that were derived from our data. First, in our study, we examined patients with rheumatic disease under GC therapy without previous treatment for osteoporosis. In previous studies on postmenopausal osteoporosis in particular an increase in resorption markers was described. Here we only found low correlations between bone markers and BMD (lumbar spine femoral neck). This result can possibly be explained by the pathophysiology of GC-induced osteoporosis. The greatest loss of bone is observed within the first 6 months after the start of GC therapy. This is followed by a steady-state phase of bone metabolism [1, 13]. The patients we examined had been treated with GCs for an average of 4 years, which means that this steady-state phase had clearly already been achieved by the majority of the patients, as reflected by the bone markers.

Second, it is a matter of fact that patients with rheumatic disease under GC therapy have an elevated risk of osteoporosis. This is also reflected by our data. We determined reduced BMD (osteopenia/osteoporosis) in 82.8% of the patients investigated. These patients require early osteoporosis therapy in accordance with the current guidelines (NOS/ACR). However, these guidelines are not put into practice consistently in daily routine. Hart and Green [15] recorded the prescription of drugs for the prevention of GC-induced osteoporosis in London and found that the applied osteoporosis prophylaxis tended to reflect the local conditions rather than the guidelines of national osteoporosis associations. This observation accentuates the fact that guidelines on the diagnosis and therapy of GC-induced osteoporosis and their consistent implementation are urgently necessary. Our paper could contribute to recommendations being drawn up for GC-induced osteoporosis, similar to those already available for postmenopausal osteoporosis from the Committee of Scientific Advisors of the International Osteoporosis Foundation on the use of bone metabolism markers [4]. However, our results point to the limited importance of determining the bone markers we investigated in GC-induced osteoporosis.

However, we have to notice critically that, in the investigation of the relationship between bone markers (dynamic markers of bone formation and degradation) and BMD (the result of the formation and degradation process over a long time) at one time point, a strong correlation between current and long-term aspects is difficult to assess. Thus, to clarify this issue, one must look for the difference in BMD (Δ BMD) and the mean of the bone markers (or integral) using multiple measuring points over a certain time period.

Conclusion

A general recommendation for the routine use of bone markers instead of BMD measurements cannot be made from a cost-benefit point of view mainly because of the limited predictive power (low correlation coefficients, incomplete correlation with different sites of BMD measurement), but these markers may be of value in making a decision for adequate therapeutic procedures and in estimating the therapeutic response.

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