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REVIEW

Bone turnover markers in Paget's disease of the bone: A Systematic review and meta-analysis

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Abstract
Summary The aim of this systematic review and meta-analysis is to study the utility of the commonly used bone turnover markers in evaluating disease activity in patients with Paget's disease of bone before and after treatment with bisphosphonates. We found good correlation between the bone turnover marker concentrations and disease activity assessed by bone scintigraphy.
Introduction Paget's disease of bone is a common skeletal disorder of the elderly. Bone turnover marker concentrations are used for diagnosis and follow-up. We aimed to compare the available bone turnover markers and determine their utility in assessing disease activity when compared to quantitative bone scintigraphy.
Methods We conducted a systematic review and meta-analysis searching MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus. We evaluated total alkaline phosphatase (total ALP), bone-specific alkaline phosphatase (bone ALP), procollagen type 1 amino-terminal propeptide (P1NP), serum, and urine C-terminal telopeptide (uCTx and sCTx, respectively), and urine N-terminal telopeptide (uNTx). The main outcome of interest was the correlation of disease activity with concentrations of bone turnover markers in Paget's disease patients before and after treatment with bisphosphonates. Correlation coefficients were pooled across studies using the random effects model.
Results We included 17 observational studies and one trial reporting on 953 patients. Prior to treatment, all studied bone turnover markers had moderate to strong correlation with scintigraphic indices (correlation coefficients ranging from 0.58 to 0.80) with no statistically significant difference between the bone turnover markers overall (p=0.08). P1NP, uNTx, and bone ALP tend to have higher correlation with scintigraphy. After starting treatment with bisphosphonate, there was moderate to strong correlation with disease activity with all markers except bone ALP (correlation coefficients ranging from 0.43 to 0.70).
Conclusion The findings of this meta-analysis suggest the Paget's disease activity is best monitored by following P1NP levels. However, total ALP, bone ALP, and uNTx are good alternatives as markers of disease activity in untreated patients. Total ALP and uNTx can be useful in following patients with Paget's disease after treatment if P1NP is not available. Clinicians, however, should take availability, cost, and the presence of liver disease into consideration when deciding which bone turnover marker is most appropriate when evaluating patients with Paget's disease.

Keywords Bone turnover markers · Paget · Scintigraphy · Total alkaline phosphatase

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Introduction

Paget's disease of bone is a common skeletal disorder of the elderly. This disorder could be isolated to one bone

(monostotic) or affecting multiple bones (polyostotic). Paget's disease is slightly more common in men compared to women and the prevalence is highest among the elderly [1]. The most frequently affected sites are the pelvis, vertebrae, and the femur [2]. The prevalence of this disease significantly differs by geographic region [1]. The highest rate has been reported in the UK (5.4 %) and the lowest in Japan [1]. Prevalence rate of pelvic Paget's disease in the US among patients older than 65 years is 2.3 % based on a population-based study [3]. The fact that relatives of patients with Paget's disease are at increased risk of experiencing the disease [4, 5] and the effect of geographic distribution suggest a genetic and environmental component to its pathophysiology. Studies have shown that a high proportion of patients with familial cases of Paget's disease have mutations in the sequestosome 1 (SQSTM1) gene [6, 7].

Plain radiographs are the primary method to diagnose Paget's disease. However, when these are equivocal, computed tomography can be used to evaluate the internal bone structure and confirm the diagnosis [8, 9]. Bone scintigraphy is more sensitive than plain radiographs in detecting active pagetic lesions [9–11].

Because Paget's disease is characterized by a high rate of bone remodeling that results in abnormal bone formation [12], biochemical markers of bone turnover have widely been utilized as an objective tool to evaluate disease activity and monitor response to treatment. Currently, the most commonly used treatment for Paget's disease is bisphosphonates. Treatment with a bisphosphonate often leads to normalization of bone turnover markers [13]. Due to its good sensitivity, low cost, and wide availability, total alkaline phosphatase (total ALP) has been the most frequently used marker to detect Paget's disease activity and follow its progression. There are many other bone turnover markers that have been utilized to assess disease activity. Bone-specific alkaline phosphatase (bone ALP) and procollagen type 1 amino-terminal propeptide (P1NP) are markers of osteoblast activity [14–16]. On the other hand, markers of osteoclast activity include serum and urine C-terminal telopeptide (sCTx and uCTx, respectively) and urine N-terminal telopeptide (uNTx). In this systematic review and meta-analysis, we summarize the available evidence regarding the utility of markers of bone turnover in evaluating disease activity in patients with Paget's disease prior to treatment and during the follow-up period after treatment.

Methods

Reporting this systematic review is based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [17]. This review was conducted based on a priori established protocol.

Inclusion and exclusion criteria

Eligible studies were any type of study that evaluated the utility of using bone turnover markers in patients diagnosed with Paget's disease. In this review, we consider bone scintigraphy as the gold standard to determine disease activity. The bone turnover markers of interests are total ALP, bone ALP, P1NP, sCTx and uCTx (alpha or beta isoforms), and uNTx. Because we are also aiming to evaluate the usefulness of these markers in assessing disease activity after treatment with bisphosphonates, studies that evaluated the utility of bone turnover markers in patients undergoing bisphosphonate treatment are included. Studies that do not report the outcome of interest (correlation coefficient factor between the markers and bone scintigraphy or sensitivity of bone turnover markers to detect Paget's disease) are excluded. We also excluded publications without original data (clinical reviews and editorials), as well as studies with no available full-text paper. No language or country restrictions are used.

Data sources and search strategy

A comprehensive search of several databases from each database's earliest inception to October 2012, which was updated to include studies to December 2014, in any language, was conducted. The databases include Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for serum and urinary biological markers of Paget's disease. The electronic search was supplemented with manual search and review of bibliographies of included studies. The actual strategy is detailed as Appendix 1.

Study selection and data extraction

Pairs of reviewers independently assessed each abstract for eligibility. Disagreement yielded an automatic inclusion in the upper level of screening. Included studies were retrieved as full text and they were screened in duplicate. Disagreement at this level was resolved by consensus. Information (baseline characteristics and results) were extracted by reviewers independently in duplicate. The PI resolved conflicts in the reviewers' data by referring to the full-text article.

Reviewers independently extracted study details from the full-text articles using a predesigned online form. The following data were abstracted: study design, country, patient characteristics (number of patients in each arm, sex, and age), follow-up period, details about their Paget's disease (treatment, disease progression, and/or response to treatment definition and markers used).

Assessment of study quality

The quality of included observational studies was assessed using the Newcastle–Ottawa scale [18] by determining outcome ascertainment, adjustment for confounders, and proportion of patients lost to follow-up as well as sample selection. Quality of the randomized controlled trials (RCT) was assessed using Cochrane's Collaboration's tool [19] by determining the randomization method, blinding, allocation concealment, lost to follow–up, and source of funding.

Statistical analysis

The main outcome of interest was the correlation between bone turnover marker levels and scintigraphic activity at baseline and after bisphosphonate treatment. The correlation coefficient value and the number of subjects included in the study analysis were extracted. The correlation coefficient values range from −1,+1. We considered the correlation to be weak if the correlation coefficient value is less than 0.3, moderate if the value is ranged between 0.3 and 0.7, and strong if the correlation coefficient value is greater than 0.7 [20].

Other outcomes of interest were the correlation between different bone turnover marker levels and sensitivity of bone turnover markers to detect disease activity. Correlation coefficients were pooled across studies using the random effects model. Statistical analysis was conducted using Comprehensive Meta-Analysis (CMA) software.

Results

Study selection

The search identified 637 abstracts of which 18 studies met all the inclusion criteria and are included in this systematic review (see Fig. 1). Seven of the included 18 studies assessed the utility of bone turnover markers in patients with Paget's disease before treatment [8, 9, 21–25]. Three were cross-sectional, two cohort prospective, one cohort retrospective, and one case-control study. The characteristics of the studies are summarized in Table 1. Six other studies followed patients from the period prior to treatment throughout treatment [10, 11, 26–29]. One is a randomized controlled trial (RCT) [29], and the rest are cohort prospective studies. The total number of untreated patients with Paget's disease in these 12 studies was 483.

Five studies evaluated the role of bone turnover markers in managing patients with Paget's disease only after treatment [30–34]. One of these five studies was a prospective clinical trial [30], whereas the rest were cohort prospective studies. In total, the 11 studies included 401 patients with Paget's disease. The characteristics of the 11 studies are summarized in Table 2. The RCT compared treatment with ibandronate to placebo. Patients in other studies received several bisphosphonates including tiludronate, zoledronate, and pamidronate. Bone scintigraphic indices (visual or quantitative) were the methods used to assess Paget's disease activity in all studies.

Of the studies that evaluated urine and serum CTx, five evaluated the beta isoform [8, 11, 21, 29, 35], one studied both alpha and beta isoforms [36], and one study did not report which isoform was evaluated [24].

Comparative analysis of bone turnover markers in untreated patients

We conducted a meta-analysis on studies that evaluated the correlation between disease activity assessed by quantitative scintigraphy and bone turnover marker concentrations (Fig. 2). All bone turnover markers had moderate to strong correlation with scintigraphic indices. There is no statistically significant difference between the markers overall (p=0.08). P1NP, uNTx, and bone ALP tend to have higher correlation with scintigraphy at baseline.

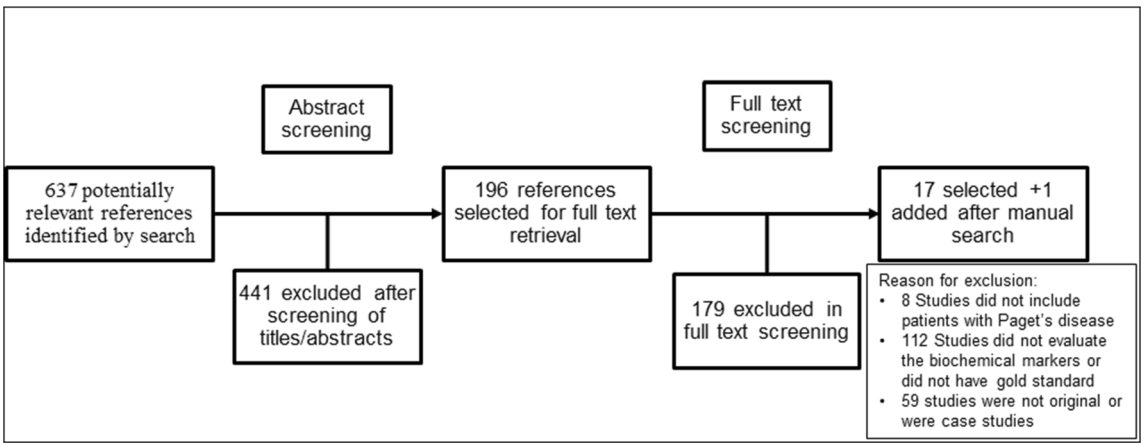

Fig. 1 Screening process

Table 1 Baseline characteristics of the included studies that evaluated the utility of bone turnover markers in patients with untreated Paget's disease

Study label	Type of study	Objective and inclusion/exclusion criteria	Description of study arms	Markers studied	Main findings
Alvarez et al. [8]	Observational prospective	– To evaluate the components of biological variation of the new markers of bone turnover in patients with Paget's bone disease and to compare the results with data obtained in healthy subjects.	– 15 Stable and asymptomatic Paget's disease patients (mean age: 63±10 years, 67 % males).	All markers are useful in monitoring.	
		– Normal renal and liver function. None of the patient had been treated with any medication before and/or during the study.	– 12 Healthy premenopausal women (mean age: 40±6.2 years, all women).	Total ALP	– Serum bone ALP and P1NP seem to be the markers that best reflect significant change in activity.
				P1NP	
				sCTx	– Serum beta CTx showed the lowest biological variability and critical difference in pagetic patients.
Woitge et al. [24]	Case-control	– Clinical assessment of novel serum markers of bone resorption and comparison with established urinary indices.	– 18 Paget's patients (age not reported, 56 % males)	– Patients with Paget's disease had elevated concentrations of all urine and serum markers. Sensitivity: total ALP 100 %, uNTx 94 %, uCTx 64 %, and sCTx 54 %	
		– Patients with Paget's disease confirmed by radiographic, scintigraphic, and laboratory findings. None of the patients had received treatment for at least 6 months before sample collection.	– 88 Healthy subjects (age not reported, 31 %males)	uNTx	– Highest diagnostic validity with U-NTx.
				uCTx sCTx	– Correlation between sCTx and uCTx was found to be r=0.63.
Alvarez et al. [21]	Cross-sectional	– To evaluate the relationship between bone turnover markers of bone turnover and bone scan indices of disease activity, as well as to analyze their variations based on skeletal involvement in Paget's disease.	– 51 Paget's patients (mean age: 67±11 years, 60 % males)	– Patients with polyostotic disease showed significantly higher values for all the bone turnover markers of bone turnover than did patients with monostotic disease.	
		– Liver and kidney function test results were normal in all patients, and none had been treated with bisphosphonates, calcitonin, or plicamycin for a period of 6 months before the study.	– 59 Healthy controls (age- and sex-matched)	– Patients with skull involvement (monostotic or polyostotic) showed higher values of all bone turnover markers of bone formation than did patients without skull involvement.	
				– All markers of bone turnover were significantly correlated with both scintigraphic indices.	
				Total ALP	– Was elevated in 76 % of the patients.
				Bone ALP	– Was elevated in 82 % of the patients.
				uNTx	– Among the patients with Paget's disease, UNTx was the most sensitive marker of bone resorption since it showed the highest frequency of increased values (96 %).
				P1NP	– Most of the patients with mild disease (71 %) showed increased serum P1NP values. Serum P1NP was the marker with highest correlation coefficient. r=0.7784
					– P1NP was increased in 94 % of the patients.

Table 1 (continued)

Study label	Type of study	Objective and inclusion/exclusion criteria	Description of study arms	Markers studied	Main findings
Pons et al. [22]	Observational prospective	– To develop a quantitative method for the scintigraphic assessment of Paget's disease activity in bone. – No treatment of Paget's disease for a year before the study. Patients with renal or hepatic disease were excluded.	– 20 Paget's patients (mean age: 65 years, 75 % males)	Serum P1NP was the most sensitive marker of bone formation, and urinary NTx was the most sensitive marker of bone resorption.	
				Total ALP	– 80 % of the patients had increased TOTAL ALPTOTAL ALP level.
				P1NP	– All patients had increased levels of P1NP.
					– Correlation with scintigraphy P1NP r=0.69.
				uNTx	– Almost all patients had increased levels of NTx (19/20).
					– Correlation with scintigraphy NTx r=0.63.
Bonnin et al. [9]	Cross-sectional	– To evaluate circulating type I procollagen propeptides in patients with Paget's disease. – Inclusion/exclusion criteria: NR	– 80 Paget's patients (mean age: 69 years, 63 % males)	– In patients with polyostotic disease significantly higher values were found for total ALP (p=0.006) and P1NP (p=0.001).	
				– Both bone turnover markers were significantly correlated with bone scintigraphic indices (r=0.63 in total ALP and 0.6 for P1NP. p<0.001).	
				– Correlation between P1NP and total ALP r=0.8.	
				Total ALP	– Total ALP high in 76 % of the patients.
				P1NP	– P1NP high in 77 % of the patients.
Meunier et al. [23]	Cross-sectional	– To reappraise the skeletal distribution and extent of Paget's disease, to compare roentgenographic and scintigraphic findings between biochemical data and the extent of the disease evaluated from bone scintigraphy. – Only scintigraphic, roentgeographic, and biochemical data collected before treatment.	– 170 Paget's patients (mean age 65.4 years, 58 % males).	Total ALP	– Total ALP was measured in 166 patients.
					– Ten patients had normal total ALP levels.
					– Highly significant positive linear correlation between the scintigraphic index of extent and the level of serum alkaline phosphatase (r=0.66, p<0.001).
Bachiller-Corral et al. [25]	Observational retrospective	– To evaluate whether it is more difficult to diagnose patients with monostotic femoral Paget's disease.	– 188 patients with monostotic Paget's disease. 24 femoral and 164 nonfemoral (mean age 64.8 years, 49 % males).	Total ALP	– Total ALP was normal in 18.6 % of the patients (31.8 % of patients with femoral disease vs. 16.8 % of patients with monostototic disease) in other sites.

Table 2 Baseline characteristics of the included studies that evaluated the utility of bone turnover markers in patients with Paget's disease after treatment

Study label	Type of study	Objective and inclusion/exclusion criteria	Description of study arms	Bone turnover markers studied	Main findings
Reid et al. [29]	RCT	– To assess the performance of seven available markers in 20 patients with Paget's disease undergoing ibandronate therapy. – Entry to the present study required that patients had alkaline phosphatase levels at least twice the upper limit of normal	– 20 Paget's patients treated with ibandronate (mean age: 74±7, 71 % males). Treatment: 6 or 12 mg of ibandronate – 9 Paget's patients receiving placebo (mean age: 72±10, 77 % males)		– All patients (monostotic and polyostotic) showed higher mean baseline values for all markers compared with controls. – Patients with polyostotic disease showed higher mean values for all bone markers than monostotic patients. – Among markers of bone formation, serum P1NP and bone ALP showed the most marked decrease after treatment, with reduction of >60 % at both time points. – Among markers of bone resorption, urinary NTx showed the highest response after therapy, with a reduction of 68 %. – Bone scan has higher sensitivity compared to bone turnover markers. That is based on the following: In patients (4/11) who still had substantial activity on Scintigraphy, all but one had normal values for the bone turnover markers
Alexandersen et al. [10]	Observational prospective	– To assess the ability of nonisomerized collagen type I C-telopeptide fragments (alpha–alpha CTX) marker to monitor disease activity and treatment efficacy in patients with Paget's disease compared with established bone turnover markers. – All patients had normal liver and kidney functions, and none had received therapies known to influence bone turnover 2 years before entry into the study.	– 32 patients diagnosed with Paget's disease (mean age: 62.8±11.1, 47 % males). Treatment: 400 mg/day of oral tiludronate for 3 months – 48 untreated age-matched and healthy controls		– All markers correlated significantly to the SAI. The highest correlation coefficient was found for baseline values – All markers were increased in patients affected by Paget's disease compared with healthy controls. In patients with Paget's disease:
				Total ALP	– Correlation with SAI: At baseline, r^2=0.4. 6 months after treatment, 0.07.
				Bone ALP	– Correlation with SAI: At baseline, r^2=0.52. 6 months after treatment, 0.007.
				uNTx	– uNTx had the most significant increase in Paget's patients (5.8 times) compared to control. – Correlation with SAI: At baseline, r^2=0.6. After treatment, 0.49.
				P1NP	– Correlation with SAI: At baseline, r^2=0.72. 6 months after treatment, 0.47
Alvarez et al. [31]	Observational prospective	– To monitor the long-term evolution of Paget's disease activity after treatment, to analyze the predictors of long-term response to therapy, and to study the most appropriate intervals of time for monitoring the response to therapy.	– 32 Patients with Paget's disease treated with tiludronate (mean age: 62±2.1, 56 % males). Treatment: 400 mg of oral tiludronate daily for 3 months		– At entry, patients with Paget's disease showed higher mean baseline values for all markers compared with controls.

Table 2 (continued)

Study label	Type of study	Objective and inclusion/exclusion criteria	Description of study arms	Bone turnover markers studied	Main findings
		– Paget's disease diagnosed and documented by plain radiographs and bone scintigraphy. All patients were treated with tiludronate.	– 37 Matched healthy volunteers (mean age: 65±1.5, 41 % males)		– At 6 months, the mean percentage of reduction in serum levels of bone ALP was 69 %, P1NP was 68 %, and UNTX was 64 %. Whereas the mean percentage of reduction for serum total ALP was 51 %. – At 6 months, the percentage of patients with bone turnover markers within the normal range were 71 % for serum total ALP, 76 % for serum bone ALP, 65 % for serum P1NP, and 62 % for urinary NTX. Conversely, no patient presented normalized bone SAI.
				Bone ALP	– Bone ALP is the most sensitive marker for Paget's disease relapse after 24 months of discontinuing treatment (100 % of the patients with relapsed disease had an increase in their bone ALP).
Garnero et al. [32]	Observational prospective	– To measure the urinary excretion of nonisomerized (a) and beta-isomerized (beta) CTX in patients with Paget's disease treated with a bisphosphonate. – Inclusion/exclusion criteria: NR	– 25 Paget's patients (mean age: 70±7, 75 % males). Treatment: 200 or 400 pg of zoledronate – 97 age- and sex-matched controls (mean age: 71±8, 67 % males)		– The levels of all bone markers were markedly increased in untreated patients compared with age-matched healthy control subjects.
				Bone ALP	– Serum level of bone ALP deceased significantly from day 10 after treatment with one injection of zoledronic acid, and continued to be low after 2 months.
				uNTx	– Serum level of uNTx decreased significantly from day 10 after treatment with one injection of zoledronic acid (maximum reduction of 55 % after 10 days) and continued to be low after 2 months. – Among markers of bone resorption, urinary NTx was the most sensitive.
				uCTx	– Levels of beta uCTx decreased by 40 % within 5 days, then increased between days 10 and 60, and returned to baseline values by 2 months after the injection.
de la Piedra et al. [27]	Observational prospective	– To evaluate the response of different biochemical bone markers to tiludronate administration in Paget's disease of bone – Inclusion/exclusion criteria: NR	– Ten Paget's patients (mean age: 67±5, 50 % males). Treatment: 400 mg of tiludronate tablets/day for 3 months – 20 Healthy controls (mean age: 64±6, 50 % males)		– Before tiludronate administration, all patients with active Paget's disease presented significantly higher values of serum AP and bone ALP.
				Total ALP	– Total ALP decreases significantly after first and second month of treatment, then it stayed stable for another month.

Table 2 (continued)

Study label	Type of study	Objective and inclusion/exclusion criteria	Description of study arms	Bone turnover markers studied	Main findings
					– Total ALP decreased more significantly than bone ALP in the first month, and the same degree of decrease in the second month.
				Bone ALP	– Bone ALP continued to decrease significantly for the 3 months
Alvarez et al. [11]	Observational prospective	– To investigate the usefulness of bone turnover markers of bone turnover for monitoring treatment efficacy of Paget's disease of bone and also to evaluate the utility of biological variation data in choosing the best markers for assessment of biochemical response to therapy. – Symptomatic Paget's disease patients with serum total ALP above the upper limit of the normal range.	– 38 Patients with Paget's disease (mean age: 63.6±2.07, 47 % males). Treatment: tiludronate 400 mg/day for 3 months – 55 Healthy controls (age- and sex-matched)	– All patients (monostotic and polyostotic) showed higher mean baseline values for all markers compared with controls with higher levels in polyostotic compared to monostotic. – Among markers of bone formation, serum P1NP and bone ALP showed the most marked decrease after treatment – Among markers of bone resorption, urinary NTx showed the highest response after therapy, with a reduction of 68 %	
Zati et al. [34]	Observational retrospective	– To verify if the most commonly used drugs in Paget's disease, calcitonin and bisphosphonates, were able to reduce the pain and the levels of total ALP. – Patients with Paget's who were hospitalized between 1970 and 2010 at study center.	– 107 Paget's patients (mean age: 61.32±12.84, 72 % males). Treatment: 18 were treated with bisphosphonates and 27 with calcitonin; 62 did not receive treatment.	Total ALP	– Paget's disease patients with pain had significantly higher total ALP values compared to patients who did not complain of pain.
Griffith et al. [33]	Observational retrospective	– To derive, from a bone scintigram, an index which objectively measured the extent and severity of Paget's disease in the entire skeleton. – Inclusion/exclusion criteria: NR	– 40 Paget's patients (age: 74, 48–88 —median and range — 50 % males). Treatment: 25 patients were treated with pamidronate in doses from 30 to 90 mg, with between three and six intravenous infusions at two weekly intervals.	Total ALP	– Correlation with SAI: Before treatment, r=0.5. After treatment, r=0.67. – Change in total ALP to change in SAI r=0.57.
Woitge et al. [26]	Observational prospective	– To compare TOTAL ALP with new and potentially more specific markers of bone turnover in bisphosphonate-treated patients with PD – Radiologic evidence of at least one bone lesion and one of the following: total ALP>300, pain from pagetic bone lesion, or complications related to PD.	– 20 patients with active Paget's disease (mean age: 60.34±10.98, 60 % males). Treatment: ibandronate intravenous bolus injection (2 mg) or by continuous infusion (2 mg of ibandronate over 24 h).	Total ALP Bone ALP	– Serum concentration of total ALP and bone ALP were increased in all patients before treatment.
Randall et al. [30]	Prospective clinical trial	– To provide a comparison of a range of currently available markers of bone turnover in Paget's disease before and after treatment with pamidronate. – Inclusion/exclusion criteria: NR	– 69 Patients with Paget's disease divided into three groups by severity of disease (Group 1, 21 patients; Group 2, 26 patients; Group 3, 22 patients). Age range: 45–87. Treatment: 60×1, 60×4 or	– NTx had the greatest sensitivity for low levels of disease activity and was the only marker to discriminate fully from the reference range. In moderately severe disease, all our markers of interest discriminated from the reference ranges.	

Table 2 (continued)

Study label	Type of study	Objective and inclusion/exclusion criteria	Description of study arms	Bone turnover markers studied	Main findings
			60×6 mg of pamidronate at weekly intervals.	– NTx, total ALP, and bone ALP showed significant decrease in levels at 6 and 13 weeks after treatment and the change in the three of them was similar.	
				uNTx	– NTx had the greatest response to treatment.
Ulivieri et al. [28]	Observational prospective	– To evaluate the response of serum OPG levels to neridronate treatment in patients with Paget's disease of bone resistant to previous therapy. – Paget's patients not responding to clodronate.	– Nine Paget's patients who were resistant to previous treatment (mean age: 71±8.7, 44 % males). Treatment: 100 mg/day, i.v. for 2 days	Total ALP	– Total ALP and bone ALP were markedly elevated in all patients.
				Bone ALP	– Significant reduction in serum levels of total ALP and bone ALP (41.9 and 38.8 %) compared to pretreatment (after 5 months). – Correlation between the two markers: r=0.886

Patients with polyostotic disease showed significantly higher bone turnover biochemical markers compared to patients with monostotic disease patients [9, 11, 21, 29].

The sensitivity of bone turnover markers for detecting Paget's disease varied between the studies. Sensitivity of bone formation markers ranged between 77 and 100 % for P1NP, 69–100 % for total ALP and 82–100 % for bone ALP [9, 21, 22, 24, 27, 29, 37]. uNTx had the highest sensitivity of the bone resorption markers with sensitivity ranging from 94 to 100 % [22, 24, 30]. Of all the bone turnover markers, one study showed that uNTx had the greatest sensitivity for low levels of disease activity, since it was the only marker that discriminated fully from the reference range [30]. We were unable to calculate the sensitivity of simultaneously using more than one bone turnover marker, since such analysis requires individual patient data.

Correlation between bone turnover markers was studied at baseline (Fig. 3). Generally, there was a moderate to strong correlation between bone ALP, total ALP, P1NP, and uNTx. bone ALP had a strong correlation with total ALP and P1NP; but a moderate correlation with uNTx and a weak correlation with uCTx . P1NP had a strong correlation with bone ALP, uNTx, and total ALP. P1NP had a weak to moderate correlation with uCTx. Total ALP had a strong correlation with bone ALP and P1NP, but a moderate correlation with uNTx. Total ALP had a weak correlation with uCTx. uNTx had a strong correlation with P1NP, but a moderate correlation with total ALP, bone ALP, and uCTx. uCTx had weak correlation with bone ALP and total ALP, weak to moderate correlation with P1NP, and a moderate correlation with uNTx and sCTx [9, 29].

Comparative analysis of bone turnover markers in treated patients

All bone turnover marker concentrations decreased significantly after treatment with bisphosphonates. Among markers of bone formation, serum P1NP and bone ALP showed the most marked decrease after treatment. uNTx had the most marked decrease among markers of bone resorption [11, 29, 31].

We conducted a meta-analysis on studies that evaluated the correlation between disease activity after treatment assessed by quantitative scintigraphy and bone turnover marker concentrations (Fig. 4). There was moderate to strong correlation with disease activity with all markers except bone ALP. The meta-analysis detected a statistically significant difference between the bone turnover markers (p=0.019) in patients with Paget's disease after treatment. Due to the small number of studies, we are unable to assess the effect of time and magnitude of response.

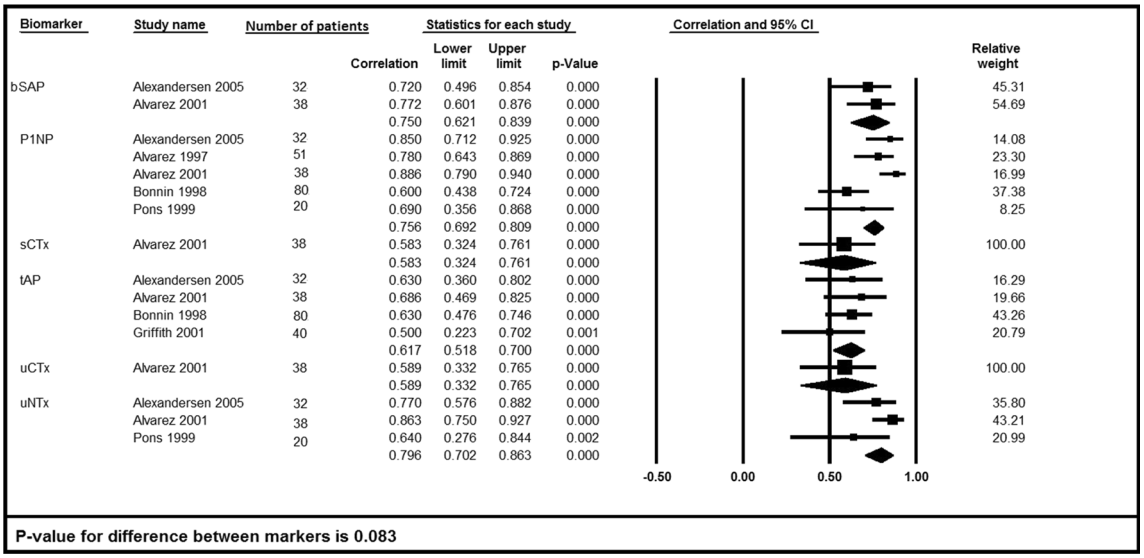

Fig. 2 Correlation between bone turnover markers and scintigraphic activity at baseline

Bone ALP

Serum concentrations of bone ALP decreased significantly from day 10 after treatment with zoledronic acid and continued to be low after 2 months [35]. It continued to decrease significantly after 3 months of treatment with tiludronate and with pamidronate [27, 30]. There was a significant reduction in the serum concentration of bone ALP after 5 months of treatment with neridronate [28]. At 6 months after treatment, Alvarez et al. [31] reported that 76 % of the patients had a normal bone ALP concentration. One study concluded that bone ALP was the most sensitive marker for Paget's disease relapse after 24 months of discontinuing treatment (100 % of the patients with relapsed disease had an increase in their bone ALP). However, the meta-analysis that we conducted showed a weak correlation between bone ALP and scintigraphic indices after treatment (r=0.24, p=0.047).

Total ALP

Serum concentrations of total ALP decreased significantly after the first and second month of treatment, then remained

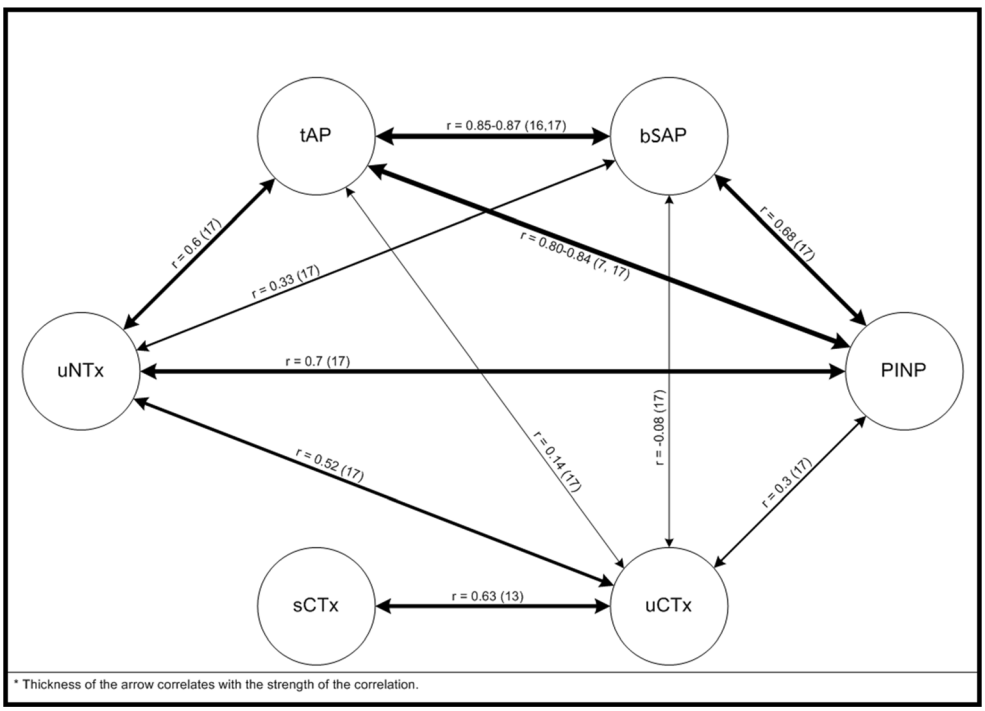

Fig. 3 Correlation between bone turnover markers of Paget's disease at baseline

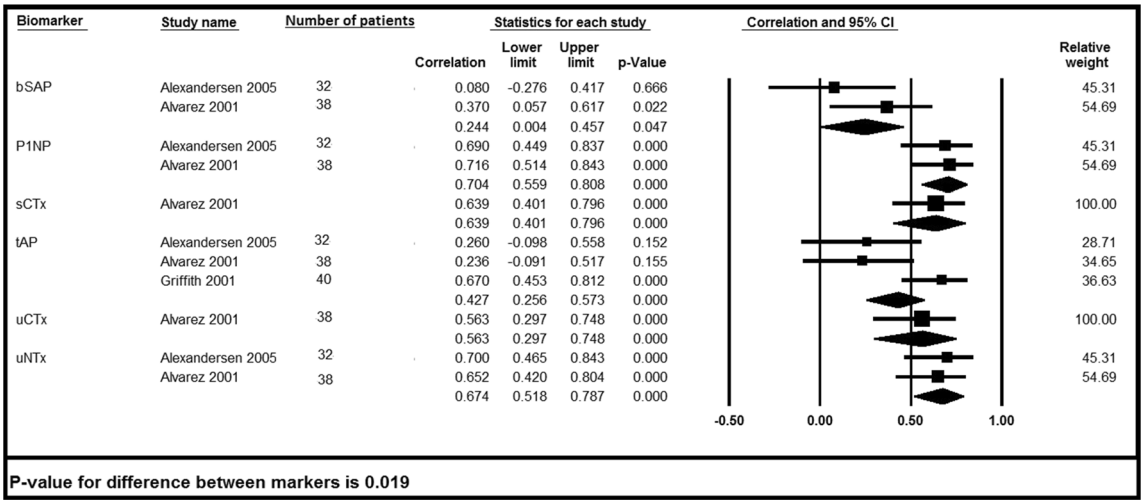

Fig. 4 Correlation between bone turnover markers and scintigraphic activity after treatment

stable for another month in patients treated with tiludronate [27]. There was a significant reduction noticed 5 months after treatment with noridronate [28]. Strong correlation was found between bone ALP and total ALP after treatment [28]. Pooling the results of the studies that reported correlation between total ALP and bone scintigraphy showed moderate correlation between total ALP and scintigraphic indices after treatment (r=0.427, p=0.000).

P1NP

Along with bone ALP, P1NP showed the most marked decrease after treatment. P1NP showed a strong correlation with scintigraphic activity after treatment (r=0.704, p=0.000) [11, 31].

uNTx

Among markers of bone resorption, uNTx showed the highest response to treatment [11, 30, 31]. uNTx concentrations decreased significantly from day 10 after treatment with one injection of zoledronic acid and continued to be reduced 2 months after treatment [35] and 6 months after treatment [11, 31]. uNTx has moderate correlation with scintigraphic activity in Paget's disease patients after treatment (r=0.674, p=0.000).

uCTx

Concentrations of uCTx decreased by 40 % within 5 days, then increased between days 10 and 60, and returned to baseline values by 2 months after one zoledronic acid infusion [35]. One study evaluated the correlation between uCTx and bone scintigraphic activity in patients with Paget's disease after treatment and showed a moderate correlation between them (r=0.563, p=0.000) [11].

sCTx

sCTx showed a significant decrease in monostotic patients only at 1 month after treatment, but continued to decrease in the first 6 months after treatment in patients with polyostotic disease, as reported by Alvarez et al. [11]. Alvarez et al. [11] reported moderate correlation between sCTx and bone scintigraphic indices in Paget's disease patients after treatment (r= 0.639. p=0.000).

One study assessed the bone turnover marker values after treatment in patients with monostotic vs. polyostotic disease. In this study, the bone turnover markers decreased significantly in both groups. However, all bone turnover marker values continued to be higher than control in patients with polyostotic disease after 6 months of treatment, whereas total ALP was the only marker that was different from the control group in patients with monostotic disease [11].

Quality assessment

One RCT was included in our systematic review [29] and had an unclear method of randomization and allocation concealment. The authors did not report whether the patients or the investigators were blinded from the interventions or outcomes (Table 3). The observational studies had overall fair quality (Table 4).

Discussion

The diagnosis of Paget's disease is often incidental during the evaluation of another health condition. The diagnosis is confirmed radiographically [38]. The best available method to evaluate disease activity is bone scintigraphy [9–11]. Measuring bone turnover markers, specifically total and bone-specific alkaline phosphatase, has been recommended and widely used by

Table 3 Quality assessment of the included RCT

Study label	Random sequence generation	Allocation concealed	Blinding of patients	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Source of study funding
Reid et al. [29]	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk

clinicians to assist in diagnosing and following patients with Paget's disease. However, these recommendations are mainly based on expert opinion or clinical experience [39]. The excessive bone remodeling that occurs in patients with Paget's disease results in nonlamellar bone formation and disorganized collagen maturation and deposition [40]. So breakdown products of type 1 collagen, such as CTx and NTx [41], as well as markers of collagen formation that result from conversion of type 1 procollagen to collagen, such as P1NP, have been widely used as markers of disease activity [42]. In this systematic review and meta-analysis, we summarized the current available evidence in regard to the usefulness of bone turnover markers in the management of Paget's disease of the bones.

Main findings and clinical implications

We found that all the bone turnover markers we evaluated have high sensitivity to pagetic bone changes considering bone scintigraphy as a gold standard to evaluate disease activity. However, normal concentrations do not completely rule out Paget's disease.

All bone turnover markers showed moderate to strong correlation with scintigraphic indices prior to bisphosphonate treatment. This suggests that bone turnover markers are good surrogate for the degree of disease activity in the untreated state.

P1NP , bone ALP, total ALP, and uNTx have good sensitivity for detecting Paget's disease. We also demonstrated that these bone turnover markers have moderate to strong correlation between each other at baseline. These facts make any of these markers a reasonable option for assessing disease activity in patients with Paget's disease at baseline. However, although the available evidence does not demonstrate clear superiority of a particular marker, the highest correlation with bone scintigraphy was found for P1NP for bone formation and uNTx for bone resorption. After treatment, the P1NP concentration demonstrated the highest correlation with disease activity. Although this makes P1NP an attractive option for monitoring response to treatment, it is not as widely available and is more expensive to perform compared to total ALP. Due to its availability and moderate correlation with bone scintigraphy, total ALP is a useful marker to assess disease activity after treatment. Total ALP remains as one of the least expensive and most available markers with the limitation of decreased accuracy in patients with liver disease.

Study limitations

There are multiple limitations to this review. The methods used to calculate bone scintigraphic index differed between the studies. For example, among the studies that evaluated the correlation between bone turnover markers and scintigraphic activity, Pons et al. [22], Alexandersen et al. [10], and Alvarez et al. [11] followed the same protocol in calculating the scintigraphic indices. This protocol is described in detail in the study of Pons et al. [22]. Whereas, Alvarez et al. [21], Griffith et al. [33], and Meunier et al. [23] followed different protocols. All these methods are at risk of subjectivity as well. Bonnin et al. [9] did not describe the method used to calculate bone scintigraphic index. One other limitation to our systematic review and meta-analysis is that most of the available studies in the literature are observational studies with different follow-up periods.

An important limitation to this review is that we were not able to analyze the correlation between disease activity based on the gold standard and the bone turnover marker concentrations in patients with monostotic disease vs. patients with polyostotic disease. That is because in most of the studies, even when the authors reported higher bone turnover marker concentrations in patients with polyostotic disease, they did not separately report the correlation with bone scintigraphy in patients with monostotic vs. polyostotic disease. A similar problem was recognized when we attempted to calculate the sensitivity of bone formation markers together

Conclusion

The current available evidence suggests good correlation between bone turnover marker concentrations and disease activity as assessed by bone scintigraphy in patients with Paget's disease before treatment and during follow-up of patients after bisphosphonate therapy.

Based on the findings of our meta-analysis, disease activity is best assessed by following P1NP concentrations both initially and after therapy with bisphosphonates. However, because this marker is not universally available, and due to its strong correlation with total ALP, bone ALP, and uNTx in untreated patients, these markers can be used as markers for disease activity in patients with Paget's disease before treatment.

Because of their moderate to strong correlation with disease activity after treatment, total ALP and uNTx can be

Table 4 Quality assessment of observational studies and the clinical prospective study

Study label	Type of study	Representativeness of study patients	Demonstration that outcome of interest was not present at start of study	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up (large number of drop-outs?)	Source of study funding
Alvarez et al. [8]	Observational prospective	High risk of bias (control group only consisted on women)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Not for profit
Woitge et al. [24]	Case control	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Not for profit
Alvarez et al. [21]	Cross-sectional	Low risk of bias	Low risk of bias	Low risk of bias	Unclear	Unclear	Unclear
Pons et al. [22]	Observational prospective	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Not for profit
Bonnin et al. [9]	Cross-sectional	Low risk of bias	Low risk of bias	Low risk of bias	Unclear	Low risk of bias	Not for profit
Meunier et al. [23]	Cross-sectional	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Not for profit
Alexandersen et al. [10]	Observational prospective	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk (six patients with Paget's disease withdrew in the first month	Not for profit
Alvarez et al. [31]	Observational prospective	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk (four patients withdrew and seven did not come for follow-ups)	Not for profit
Garnero et al. [32]	Observational prospective	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias (follow-up period was 2 months)	Low risk of bias	For profit (pharmaceutical)
de la Piedra et al. [27]	Observational prospective	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias (follow-up period was 3 months)	Low risk of bias	Not for profit
Zati et al. [34]	Observational retrospective	High risk of bias (included only whites with Paget's disease)	Low risk of bias	Low risk of bias	Unclear	Low risk of bias	Not for profit
Griffith et al. [33]	Observational retrospective	Low risk of bias	Low risk of bias	Low risk of bias	High of bias (median follow-up period was 123 days)	Low risk of bias	Not for profit
Woitge et al. [26]	Observational prospective	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Not for profit
Randall et al. [30]	Prospective clinical trial	Low risk of bias	Unclear	Low risk of bias	High risk of bias (follow-up was 26 weeks)	Low risk of bias	Not for profit
Ulivieri et al. [28]	Observational prospective	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias (follow-up was 5 months)	Low risk of bias	Not for profit
Bachiller-Corral et al. [25]	Observational retrospective	High risk of bias (included patients in whom lesions were confined to the femur and then compared to other monostotic lesions)	Low risk of bias	Low risk of bias	Unclear	Low risk of bias	Not for profit

useful in following patients with Paget's disease after treatment if P1NP is not available. Clinicians, however, should take availability, cost, and the presence of liver disease in consideration when deciding the bone turnover markers when following patients with Paget's disease.

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Conflicts of interest None.

Appendix 1

Search strategy

Ovid

Database(s) EMBASE 1988 to 2012 Week 42, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials October 2012, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 2012

Scopus

1 TITLE-ABS-KEY("Osteitis Deformans" or (paget W/4 bone) or (pagets W/4 bone) or "ostitis deformans")
2 TITLE-ABS-KEY("biological marker*" or biomarker* or "serum marker*" or "laboratory marker*" or "immunologicmarker*" or (surrogate W/1 endpoint*) or (surrogate W/1 "end point*") or "biologic marker*" or "immune marker*" or "clinical marker*" or "biochemical marker*" or "biological indicator*" or bioindicator* or "Alkaline Phosphatase"or "alcalic phosphatase" or "alkali phosphatase" or "alkalic phosphatase" or "alkaline monophosphoesterase" or "alkaline phosphohydrolase" or "alkaline phosphomonoesterase" or "alkalinic phosphatase" or "basic phosphatase" or "orthophosphoric monoester phosphohydrolase" or procollagen or "collagen precursor" or "proto-collagen" or protocollagen or precollagen or "collagen type 1" or "collagen 1" or "collagen i" or "type 1 collagen" or vitrogen or "type I collagen" or P1NP or P1NP or telopeptide or creatinine or creatinin or kreatinine or methylglycocyamimine or "1 methylglycocyamidine" or "1 methylhydantoin 1 imide" or "2 imino 1 methyl 4imidazolinone")
3 TITLE-ABS-KEY(serum or blood or urine or urinary)

Table. 5 Search Strategy

#	Searches	Results
1	exp Osteitis deformans/	8,314
2	exp Paget bone disease/	3,684
3	{"Osteitis deformans" or [(paget or pagets) adj4 bone] or "ostitis deformans"}.mp. (mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct)	9,113
4	or/1–3	9,113
5	exp Biological markers/	676,644
6	exp Alkaline phosphatase/	92,083
7	exp Procollagen/	10,570
8	exp Collagen type 1/	32,448
9	exp Telopeptide/	407
10	exp Creatinine/	118,160
11	exp Creatinine urine level/	4,756
12	{"Biological marker*" or biomarker* or "serum marker*" or "laboratory marker*" or "immunologic marker*" or [surrogate adj (endpoint* or "end point*")]} or "biologic marker*" or "immune marker*" or "clinical marker*" or "biochemical marker*" or "biological indicator*" or bioindicator* or "alkaline phosphatase" or "alcalic phosphatase" or "alkali phosphatase" or "alkalic phosphatase" or "alkaline monophosphoesterase" or "alkaline phosphohydrolase" or "alkaline phosphomonoesterase" or "alkalinic phosphatase" or "basic phosphatase" or "orthophosphoric monoester phosphohydrolase" or procollagen or "collagen precursor" or "proto-collagen" or protocollagen or precollagen or "collagen type 1" or "collagen 1" or "collagen i" or "type 1 collagen" or vitrogen or "type I collagen" or P1NP or P1NP or telopeptide or creatinine or creatinin or kreatinine or methylglycocyamimine or "1 methylglycocyamidine" or "1 methylhydantoin 1 imide" or "2 imino 1 methyl 4 imidazolinone").mp. (mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct)	768,378
13	or/5–12	1,184,540
14	(Serum or blood or urine or urinary).mp,fs.	6,314,072
15	13 and 14	575,158
16	4 and 15	1,558
17	exp Controlled study/	3,960,457

Table. 5 (continued)

#	Searches	Results
18	exp Evidence-based medicine/	604,669
19	Evidence-based.mp.	203,918
20	[(Control$ or randomized) adj2 (study or studies or trial or trials)].mp. (mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct)	5,070,384
21	Meta-analysis/	103,675
22	Meta-analys$.mp.	166,866
23	exp "Systematic review"/	53,999
24	(Systematic* adj review$).mp.	126,592
25	exp Guideline/ or exp Practice guideline/	302,274
26	Guideline$.ti.	96,654
27	exp Case study/	1,616,370
28	Follow-up studies/	1,103,668
29	exp Cohort studies/	1,445,672
30	exp Longitudinal study/	938,880
31	exp Retrospective study/	720,166
32	exp Prospective study/	599,179
33	exp Observational study/	33,478
34	exp Comparative study/	2,338,205
35	exp Clinical trial/	1,596,318
36	exp Evaluation/	1,155,893
37	exp Twins/	42,548
38	exp Validation study/	36,126
39	exp Experimental study/ or exp field study/ or in vivo study/ or exp Panel study/ or exp Pilot study/ or exp Prevention study/ or exp Quasi experimental study/ or exp Replication study/ or exp Theoretical study/ or exp Trend study/ or exp Multivariate analysis/ or clinical study/	1,777,028
40	[(Clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational or multivariate) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)].mp.	7,532,086
41	("Case study" or "case series" or "clinical series" or "case studies").mp. (mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct)	178,781
42	exp Multivariate analysis/	274,699
43	or/17–42	14,086,263
44	16 and 43	803
45	From 16 keep 664–1,504	841
46	Limit 45 to (clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IVor clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or randomized controlled trial or twin study or validation studies) [Limit not valid in EMBASE, CCTR, CDSR; records were retained]	199
47	44 or 46	803
48	Limit 47 to (editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or dictionary or directory or interactive tutorial or lectures or legislation or news or newspaper article or patient education handout or periodical index or portraits or published erratum or video–audio media or webcasts) [Limit not valid in EMBASE, Ovid MEDLINE (R),Ovid MEDLINE (R) In-Process, CCTR, CDSR; records were retained]	28
49	47 not 48	775
50	Limit 49 to animals [Limit not valid in CCTR, CDSR; records were retained]	56
51	Limit 50 to human [Limit not valid in CCTR, CDSR; records were retained]	54
52	50 not 51	2
53	49 not 52	773
54	From 16 keep 1,505–1,558	54
55	53 or 54	794
56	Remove duplicates from 55	571

4 TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*) or random* or "latin square" or crossover or "cross-over" or placebo* or (doubl* N5 blind*) or (doubl* N5 mask*) or (singl* N5 blind*) or (singl* N5 mask*) or (tripl* N5 blind*) or (tripl* N5 mask*) or (trebl* N5 blind*) or (trebl* N5 mask*) or "comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort

survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey" or "retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis" or "incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis" or "observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies" or "clinical study" OR "clinical trial" or "evaluation study" OR "evaluation survey" OR "evaluation analysis" or "twin study" OR "twin survey" OR "twin analysis" or "validation study" OR "validation survey" OR "validation analysis" or "experimental study" OR "experimental analysis" or "field study" OR "field survey" OR "field analysis" or "in vivo study" OR "in vivo analysis" or "panel study" OR "panel survey" OR "panel analysis" or "pilot study" OR "pilot survey" OR "pilot analysis" or "prevention study" OR "prevention survey" OR "prevention analysis" or "replication study" OR "replication analysis" or "theoretical study" OR "theoretical analysis" or "trend study" OR "trend survey" OR "trend analysis" or "multivariate analysis")

5 1 and 2 and 3 and 4

6 PMID (0*) OR PMID (1*) OR PMID (2*) OR PMID (3*) OR PMID (4*) OR PMID (5*) OR PMID (6*) OR PMID (7*) OR PMID (8*) OR PMID (9*)

7 5 and not 6

8 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

9 7 and not 8

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