OSTASE immunoassay for the mass measurement of serum bone alkaline phosphatase

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MSAC application 1044

Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Australian Government Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Kristina Coleman, Elizabeth Barr, Sally Wortley and Davina Ghersi from the NHMRC Clinical Trials Centre, University of Sydney, and the Members of the Ostase Supporting Committee. The report was endorsed by the Australian Government Minister for Health and Ageing on 8 August 2003.

Publication approval number: 3360

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Executive summary

The procedure

Ostase is a diagnostic laboratory test used to determine the mass measurement of bone alkaline phosphatase (BALP). Three variants of Ostase are available: Tandem-R Ostase, Tandem-MP Ostase and Access Ostase. Access Ostase is a paramagnetic particle chemiluminescent immunoassay for the use with the Access Immunoassay System. Access Ostase is an automated test and is likely to be more commonly used in Australia, as it has superseded both the manually run Tandem-R and Tandem-MP Ostase tests. Serum BALP is a glycoprotein found on the surface of osteoblasts, and its amount generally reflects rates of bone formation in skeletal tissue. However, owing to the balance between bone formation and bone resorption, BALP measurements provide an indication of overall bone metabolism.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Australian Government Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision-making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre, University of Sydney, was engaged to conduct a systematic review of literature on Ostase. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of Ostase

This review assesses the clinical effectiveness of Ostase for four clinical indications: Paget's disease of bone, renal osteodystrophy, prostate cancer and osteoporosis. Specific clinical questions were formulated from information on current clinical practice (ie, common usage of BALP tests in Australia) and the purpose of the test (eg, the diagnosis of disease or evaluation of treatment). The specific components of the clinical questions addressed by this review are summarised in Table 1. The actual questions are presented under 'The research questions' on page 7.

Table 1 Components of the clinical questions reviewed

Patient group	Indication	Incremental or replacement?	Comparator	Reference standard
Paget's disease	1. Diagnostic work-up 2. Treatment monitoring	1. Incremental 2. Replacement	TALP	1. Bone scans, X-rays 2. Long-term clinical outcomes, time to recurrence, relief of symptoms
Renal osteodystrophy	1. Differentiation of the different patterns of bone disease 2. Treatment monitoring	Incremental	Other biochemical markers	Bone biopsy/imaging
Prostate cancer	1. Diagnosis of bone metastases 2. Treatment monitoring	Incremental	PSA and TALP	1. Bone scans, X-rays 2. Pain relief, long-term clinical outcomes
Osteoporosis	1. Assessment of fracture risk to inform treatment decision 2. Assessment of response to treatment	Incremental	DEXA and other biochemical markers	DEXA, fracture

Abbreviations: DEXA, dual X-ray absorptiometry; PSA, prostate-specific antigen; TALP, total alkaline phosphatase

Clinical need

Prevalence and incidence rates of the metabolic bone diseases reported on in this review were difficult to ascertain, as Australian population data were limited. It is estimated that 3 to 4 per cent of people aged over 40 years have Paget's disease of bone, but recent studies indicate that the incidence may be decreasing. Renal osteodystrophy may present in several different forms. A large multi-centre European study indicated that of patients with a glomerular filtration rate (GFR) of 15–50 mL/min, 55 per cent presented with osteitis fibrosa or hyperparathyroid bone disease, 14 per cent with mixed osteodystrophy, 1 per cent with osteomalacia and 5 per cent with adynamic bone disease. Prostate cancer is the most common malignant cancer among males in Australia, and since the early 1990s the incidence rate has increased. In 1999, approximately 10,232 cases were reported, representing an age-standardised incidence rate of 110 per 100,000 population. Prevalence estimates of osteoporosis vary considerably, ranging from 155,000 to 1.8 million. Low-impact vertebral fractures and hip fracture following a fall are common consequences associated with osteoporosis, and can lead to pain, deformity, loss of mobility and sometimes death. Large prospective studies conducted in Australia indicate that the annual incidence of fractures ranges between 50,000 and 75,000 in people aged 60 years and over.

Existing biochemical tests for metabolic bone diseases

The following biochemical tests relevant to the diagnosis and monitoring of disturbances of bone metabolism are included in the Medicare Benefits Schedule: calcium, phosphate and TALP (66500), isoenzymes of alkaline phosphatase (66641), products of collagen breakdown (66773, 66776), calcitonin and parathyroid hormone (66695), hydroxyproline (66773, 66776, 66752) and PSA (66659).

Performance characteristics

Six reports have evaluated the performance characteristics of the three Ostase tests compared with each other or with the existing test, electrophoresis, which measures BALP and is available on the Medicare Benefits Schedule (MBS). In the determination of serum BALP levels, a reasonably strong correlation was reported among the Ostase tests and between the Ostase tests and electrophoresis. However, no information is available on the sensitivity and specificity of the Ostase tests compared with each other or with Electrophoresis. About 10 per cent cross-reactivity of BALP with alkaline phosphatase of liver origin was reported; this may limit the utility of this test in patients with significant elevations of liver alkaline phosphatase (LALP).

Safety

Ostase is an *in vitro* diagnostic laboratory test that measures BALP in human sera. As such, there is no safety risk to patients. Laboratory staff and organisations intending to use the Ostase laboratory kit should ensure the safe handling of blood and other fluids as outlined in the health and safety guidelines of the National Pathology Accreditation Advisory Council.

Effectiveness

Diagnostic accuracy

The conclusions regarding the diagnostic accuracy of BALP for Paget's disease of bone, renal osteodystrophy, prostate cancer and osteoporosis are based on a small number of studies. Many of the studies also show methodological biases, which further limit the extent to which inferences can be applied to the wider clinical population. On the basis of the evidence available, it would appear that Ostase has the potential to be useful as a supplementary test in the diagnosis of Paget's disease, differentiation of renal osteodystrophy, diagnosis of bone metastases of prostate cancer, and monitoring treatment in women with osteoporosis. However, supportive evidence of the diagnostic accuracy of Ostase is required from larger, more representative studies.

Impact on clinical decision-making and health outcomes

As no studies were retrieved that specifically assessed the role of Ostase in clinical decision-making or on patient outcomes for Paget's disease of bone, renal osteodystrophy, prostate cancer or osteoporosis, it was not possible to assess its impact in these areas. Therefore, the clinical value of the determination of BALP by Ostase was not adequately demonstrated in the studies reviewed to date.

Cost-effectiveness

The price suggested by the applicant ($24.35) for Ostase would be equivalent to the Schedule Fee for existing biochemical bone marker tests that measure the products of collagen breakdown, listed on the MBS (items 66773 and 66776).

However, as the effectiveness of Ostase has yet to be conclusively determined, it is not possible to perform an economic analysis of its role in any of the indications assessed.

Although a number of studies reported that Ostase may accurately measure BALP, there is currently insufficient evidence to suggest that Ostase provides any benefit to patients as a replacement or incremental test for Paget's disease of bone, renal osteodystrophy, prostate cancer or osteoporosis.

Recommendation

Since there is currently insufficient evidence pertaining to the effectiveness and cost-effectiveness of Ostase diagnostic laboratory tests (Tandem-R Ostase, Tandem-MP Ostase and Access Ostase) in the diagnosis and monitoring of treatment in Paget's disease of bone, renal osteodystrophy, bone metastases of prostate cancer and osteoporosis, MSAC recommended that public funding should not be supported at this time for these tests.

The Australian Government Minister for Health and Ageing accepted this recommendation on 8 August 2003.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of Ostase a laboratory test that measures the content of the bone isoenzyme of alkaline phosphatase (BALP) as a marker of bone turnover. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC takes an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for the suitability of Ostase as a test for Paget's disease of bone, renal osteodystrophy, prostate cancer and osteoporosis.

Background

Overview

Assessing bone metabolism

Bone is a specialised connective tissue composed of cells and an extracellular matrix, and is maintained through bone remodelling. Bone remodelling is characterised by two opposite activities: formation and resorption. Bone formation depends on osteoblasts, which are bone-lining cells responsible for the production of the bone matrix constituents: collagen and ground substances. Bone resorption depends on osteoclasts (giant multinucleated cells), which are usually found in contact with calcified bone surfaces and within the bone lacunae, which result from their own resorptive activity. Most of the metabolic bone diseases are characterised by an alteration in the bone resorption/formation balance (Christenson 1997; Kanis 1998).

The rate of formation or resorption of the bone matrix can be assessed by measuring markers of bone turnover. These markers are by-products of bone metabolism that are found in the bloodstream, some of which are excreted in urine (Christenson 1997; Delmas 1990). A summary of the most common biochemical markers of bone turnover is shown in Table 2.

Table 2 Biochemical markers of bone turnover

Formation markers				Resorption markers			
Marker	**Abbreviation**	**Collection**	**Assay**	**Marker**	**Abbreviation**	**Collection**	**Assay**
Total alkaline phosphatase	TALP	Serum	IRMA	Hydroxyproline	Hyp	Urine	
Bone-specific alkaline phosphatase	BALP	Serum	IRMA, ELISA	Calcium	Ca	Urine	
Osteocalcin, bone Gla-protein	OC	Serum	RIA, ELISA	Pyridinoline	Pyd	Urine	EIA
Carboxy-terminal propeptide of type I procollagen	PICP	Serum	RIA	Deoxy-pyridinoline	Dpy	Urine	EIA, RIA
Carboxy propeptide of type 1 collagen	ICTP	Serum	RIA	Type 1 collagen cross-linked carboxy-terminal telopeptide	CTx	Urine / serum	ELISA, ICMA
Amino-terminal propeptide of type I procollagen	PINP	Serum	ICMA, IRMA	Type 1 collagen cross-linked amino-terminal telopeptide	NTx	Urine / serum	ELISA
				Tartrate-resistant acid phosphatase	TRAP	Serum	

Abbreviations: CTx, c-terminal telopeptide; Dpy, deoxypyridinoline; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; Gla, gamma-carboxyglutamic acid; ICMA, electrochemiluminescence immunoassay; IRMA, immunoradiometric assay; NTx, n-terminal telopeptide; RIA, radioimmunoassay.

Source: Table modified from Nelson et al (2001).

The measurement of total alkaline phosphatase (TALP) in the serum is a common, relatively simple and inexpensive test to measure bone turnover rate. TALP comprises four main types, reflecting bone, liver, intestinal and placental sources. Its use for the

measurement of bone metabolism is therefore limited in patients with concomitant liver disease or pregnancy, as TALP measures will reflect levels of all types of alkaline phosphatase. In these patients it is not possible to determine whether raised TALP reflects changes in bone metabolism or other conditions. In response to this problem, tests that specifically measure the bone isoform – bone alkaline phosphatase (BALP) – have been developed (Delmas 1990).

BALP is a glycoprotein found on the surface of osteoblasts, and therefore its amount generally reflects rates of bone formation in skeletal tissue. Owing to the coupling mechanism between bone formation and resorption, BALP measurements provide an indication of overall bone metabolism (Christenson 1997; Delmas 1990). Historically, several methods have been used to indirectly measure serum BALP, including heat inactivation (Whitby & Moss 1975), agarose gel electrophoresis (Onica, Sundblad, & Waldenlind 1986; Rosalki & Foo 1984), wheat germ lectin precipitation (Onica, Sundblad, & Waldenlind 1986; Rosalki & Foo 1984) and high-performance liquid chromatography (Magnusson et al 2001).

Many of these methods have not received widespread acceptance as they are both technically cumbersome and often exhibit poor resolution in the differentiation between liver and bone isoforms (Withold, Schulte, & Reinauer 1996). Nevertheless, electrophoresis is available for semi-quantification of the bone isoform and isoenzyme and is listed on the MBS. Immunoassays using monoclonal antibodies that preferentially distinguish between bone and liver isoforms have been developed and may provide an alternative to electrophoresis. These immunoassays measure BALP directly either by determining the enzymatic activity (Alkphase B) or by mass measurement (Tandem-R Ostase, Tandem-MP Ostase, Access Ostase) of the bone isoform. Table 3 outlines the current and new methods available to measure serum BALP.

Table 3 Current and new methods available in Australia for quantifying bone alkaline phosphatase (BALP) in human serum

	Current assay	New assays			
Test name	–	**Access Ostase**	**Tandem–R Ostase**	**Tandem–MP Ostase**	**Alkphase–B**
Company	–	Beckman Coulter	Hybritech/	Beckman Coulter	Metra Biosystems
Method	Electrophoresis	Chemiluminescent	IRMA[a]	ELISA[b]	ELISA
Measures	Enzyme activity (U/L)	Protein mass (µg/L)	Protein mass (µg/L)	Protein mass (µg/L)	Enzyme activity (U/L)

Abbreviations: U, measure of enzyme activity, usually the conversion of 1 µmol of substrate per minute under specified conditions.
[a] IRMA, immunoradiometric assay.
[b] ELISA, enzyme-linked immunosorbent assay.

The applicant for this report has requested that the immunoassay for the mass determination of BALP be considered for funding under the MBS. This review focuses on the evaluation of the safety and effectiveness of Tandem-R Ostase, Tandem-MP Ostase and Access Ostase to measure BALP. Alkphase-B, which is an immunoassay that measures enzymatic activity of BALP rather than mass, is not included in this review.

Access Ostase is an automated test and is likely to be more commonly used in Australia, as it has superseded both the manually run Tandem-R and Tandem-MP Ostase tests. Tandem-R, the earliest of the three tests, is difficult for laboratories to use, as it requires the handling and disposal of radioactive material. Tandem-MP replaced Tandem-R, as it

uses an enzyme rather than a radioisotope. However, as Tandem-MP is a manual test it is not used as widely as the newer, automated Access Ostase test.

Structure of the review

This review assesses the safety, effectiveness and cost-effectiveness of the mass measurement of BALP in patients with, or suspected of having, metabolic bone disease. The specific indications include Paget's disease of bone, renal osteodystrophy, bone metastases from prostate cancer and osteoporosis. In order to assess whether each Ostase test should be evaluated separately or in combination, it is important to determine the degree of agreement between each of the tests. Furthermore, as Ostase is a potential replacement test for electrophoresis (the current method funded under the MBS), it is necessary to establish whether the test results are correlated between Ostase tests and electrophoresis. Therefore, the review is structured into two parts with two aims:

1. To determine the degree of agreement between the performance characteristics of each of the Ostase tests and of the Ostase tests and electrophoresis.

2. To evaluate the safety and effectiveness of Ostase in patients with, or suspected of having, the following metabolic bone diseases – Paget's disease of bone, renal osteodystrophy, bone metastases from prostate cancer, and osteoporosis – as well as the cost-effectiveness of Ostase for diagnosing osteoporosis.

The procedure

The Access Ostase test is described in detail here, rather that the Tandem-R and Tandem-MP Ostase tests, as Access Ostase is a newer, automated test and is likely to be more widely used by laboratories in Australia.

Access Ostase is a paramagnetic particle chemiluminescent immunoassay for use with the Access Immunoassay Systems for the quantitative measurement of BALP. The test is a one-step immunoenzyme assay. A mouse monoclonal antibody specific to BALP is added to a reaction vessel with paramagnetic particles coated with goat anti-mouse polyclonal antibodies. Calibrators, controls and samples containing BALP are added to the coated particles and bind to the anti-BALP monoclonal antibody. Following the formation of a solid phase capture antibody–BALP complex, separation in a magnetic field and washing remove materials not bound to the solid phase. A chemiluminescent substrate, Lumi-Phos* 530, is added to the reaction vessel, and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of BALP in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

The Access Ostase assay uses the same solid-phase monoclonal antibody used in the Tandem-R Ostase assay and has been standardised to provide the same clinical performance. A recent United States Food and Drug Administration (FDA) report (2000) concluded that Access Ostase is substantially equivalent to Tandem-R Ostase in the measurement of BALP in human sera.

Table 4 outlines the specific characteristics of Access Ostase.

Table 4 Characteristics of Access Ostase

Characteristics	Values
Sample type and size	Serum or plasma; 25 µL
Time to first result	30 minutes
Analytical sensitivity	0.1 µg/L
Calibration levels	0, 7, 15, 30, 60 and 120 µg/L
Broad dynamic range	0.1–120 µg/L
Open pack stability	28 days
Calibration stability	28 days
Precision	<6.5% CV

Source: Beckman Coulter Web site (http://www.beckman.com/products/testdetail/access/ostase.asp; accessed 4 September 2002).

Intended purpose

The intended purpose of the Access Ostase assay is for the quantitative measurement of BALP in patients with, or suspected of having, metabolic bone disease. This review evaluates the use of the test for four specific indications: Paget's disease of bone, renal osteodystrophy, bone metastases from prostate cancer, and osteoporosis.

Clinical need/Burden of disease

The burden of disease for each of the indications is outlined in the subsequent sections on Paget's disease of bone, renal osteodystrophy, prostate cancer and osteoporosis.

Existing procedures

Currently, electrophoresis receives funding under the MBS as a test to identify the presence of BALP in human sera.

Comparator

The comparator for each of the four indications is listed in Appendix E and is discussed in further detail under each of the specific clinical indications.

Reference standard

The reference standard for each of the four indications is listed in Appendix E and is discussed in further detail under each of the specific clinical indications.

Marketing status of the test

Ostase is exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*. This is because the device is an *in vitro* diagnostic test only, and is not used *in vivo*. Furthermore, Ostase does not contain material of human origin.

It is more likely that Access Ostase will be marketed in Australia than Tandem-R Ostase or Tandem-MP Ostase.

Current reimbursement arrangement

Ostase is currently not funded under the Medicare Benefits Scheme.

However, item number 66641 covers

> 'Electrophoresis of serum or other body fluid to demonstrate (…) the isoenzymes of alkaline phosphatase including the preliminary quantitation of total relevant enzyme activity'.

Approach to assessment

Expert advice

A supporting committee with expertise in clinical biochemistry, pathology, general practice, nephrology, urology, endocrinology, health economics and consumer advocacy was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

The research questions

The review team worked with members of the supporting committee to develop specific questions that would cover clinically relevant uses of Ostase in the measurement of BALP. These questions were formulated *a priori* from information on current clinical practice (ie, common usage of BALP tests in Australia) and the purpose of the test (eg, diagnosis of clinical condition or evaluation of treatment). Clinical flow diagrams (Appendix F) for each of the indications were developed in collaboration with the supporting committee and other clinical experts. The aim of these diagrams is to clarify the flow of the decision-making process for each question. The PICO (Patient, Intervention, Comparator, Outcomes) criteria (Scott et al 1995) were used to develop specific clinical questions (summarised in Appendix E), which are outlined below for each of the four clinical indications.

Paget's disease of bone

- What is the additional value of Ostase to TALP in the diagnosis of Paget's disease of bone in patients suspected to have the condition?
- What is the value of Ostase compared with TALP in the monitoring of patients who have undergone pharmacological treatment for Paget's disease of bone?

Renal osteodystrophy

- What is the additional value of Ostase to other biochemical measures in the diagnosis and differentiation of the different patterns of bone disease in patients with prolonged low renal function (GFR < 30 mL/min)?
- What is the additional value of Ostase to other biochemical measures in the monitoring of treatment in patients with renal osteodystrophy?

Prostate cancer

- What is the additional value of Ostase to prostate-specific antigen (PSA) and TALP in determining the extent of bone metastases as detected on bone scans (i) in the initial staging of disease, and (ii) during follow-up after treatment in patients with prostate cancer?

- What is the additional value of Ostase to PSA and TALP in the monitoring of therapy in patients with prostate cancer and bone metastases?

Osteoporosis

- What is the additional value of Ostase to measurement of bone mineral density (BMD) by dual X-ray absorptiometry (DEXA) in determining the risk of fracture in patients at risk of osteoporosis?

- What is the additional value of Ostase to measurement of BMD by DEXA in the monitoring of therapy in patients being treated to prevent or minimise osteoporosis?

Review of literature

MSAC's recommendations are primarily based on the findings of a systematic literature review conducted by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre. Papers were also identified from the MSAC application and by members of the MSAC Ostase supporting committee (Appendix B), which was convened to evaluate the evidence and provide expert advice. The medical literature was searched to identify relevant studies and reviews for the period between 1966 and February 2003. Searches were conducted via the electronic databases listed in Table 5.

Table 5 Electronic databases searched

Database	Period covered
Medline	1966 to week 2, Jan 2003
Pre-Medline	Feb 2003
EMBASE	1982 to week 5, Jan 2003
Current Contents	1993 to Feb 2003
Biological Abstracts	1980 to Dec 2003
International Pharmaceutical Abstracts	1970 to Jan 2003
Database of Abstracts of Reviews of Effectiveness	4th quarter 2003
Cochrane Controlled Trials Register	4th quarter 2003
Cochrane Database of Systematic Reviews	4th quarter 2003
American College of Physicians Journal Club	1991 to Sept–Oct 2003

Search strategy

The search strategy in Table 6 was used to identify papers in Medline. A similar search strategy using the same search terms was used for each of the other databases listed in Table 9.

Table 6 Medline search strategy

	Search term		Search term
1	(bone adj4 alkaline pho?phatase).mp	32	(osteomalacia adj6 renal).mp
2	Ostase.mp	33	(mixed lesion adj6 renal).mp
3	BAP.mp	34	Osteitis fibrosa.mp
4	B-AP.mp	35	Kidney diseases/ or exp kidney failure/ or exp kidney, acute/ or exp kidney failure, chronic/
5	BALP.mp	36	Exp Glomerular Filtration Rate/ or glomerular filtration rate.mp
6	B-ALP.mp	37	((kidney or renal) and dialysis).tw
7	Bone specific alkaline pho?phatase.mp	38	renal impairment.tw
8	Bone alkaline pho?phatase.mp	39	end stage renal diseas$.mp
9	(Bone adj ALP).mp	40	end stage renal failure$.mp
10	(bone adj4 ALP).mp	41	Or/28–41
11	Skeletal alkaline pho?phatase.mp	42	41 and 18
12	Skeletal specific alkaline pho?phatase.mp	43	42 not 25
13	(skeletal adj ALP).mp	44	Exp Prostate Neoplasms/
14	(skeletal adj4 ALP).mp	45	(prostat$ adj carcinoma$).mp
15	(skeletal adj4 alkaline pho?phatase).mp	46	(prostat$ adj neoplasm$).mp
16	(bone formation adj4 marker$.mp)	47	(prostat$ adj cancer$).mp
17	Biochemical marker$.mp	48	(prostat$ adj tumo?r$).mp
18	Or/1–17	49	(prostat$ adj metast$).mp
19	Exp osteitis deformans/	50	Or/44–49
20	Osteitis deforman$.mp	51	50 and 18
21	Paget?s disease$.mp	52	51 not 25
22	Or/19–21	53	exp Osteoporosis/ or exp Osteoporosis, Postmenopausal/ or osteoporosis.mp
23	Exp Animal/	54	osteop?nia.mp
24	Exp Human/	55	exp Bone Density/ or bone mineral density.mp
25	23 not (23 and 24)	56	BMD.mp or Densitometry, X-ray/
26	18 and 22	57	DEXA.mp
27	26 not 25	58	Dual energy X-ray absorptiometry.mp
28	Exp renal replacement therapy/ or exp renal dialysis/ or exp hemodiafiltration/ or exp hemodialysis, home/ or exp peritoneal dialysis/ or exp peritoneal dialysis, continuous ambulatory/ or exp kidney transplantation	59	Or/53–58
29	Exp hyperparathyroidism, secondary/ or exp renal osteodystrophy/	60	59 and 18
30	adynamic bone disease.mp	61	60 not 25
31	Renal bone disease.mp		

A list of references provided by the applicant was compared with the results of the electronic search, and non-duplicate references were included in the final reference list. Reference lists of retrieved publications were searched for additional relevant citations that were not found through the electronic search. In addition to the databases listed above, Web sites of international health technology assessment agencies were searched (Table 7) for relevant health technology assessment reports.

Table 7 Web sites of international health technology assessment agencies searched

Organisation	Web site
International Society for Technology Assessment in Health Care	www.istahc.org
International Network of Agencies for Health Technology Assessment	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (USA)	www.ohppr.state.or.us/index.html
Minnesota Department of Health (USA)	www.health.state.mn.us/htac/index.htm
ECRI (USA)	www.ecri.org
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veterans Affairs Research and Development Technology Assessment Program (USA)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (USA)	www.hstat.nlm.nih.gov
Office of Health Technology Assessment Archive (USA)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.org
Conseil d'Evaluation des Technologies de la Santé du Québec (Canada)	www.mss.gouv.qc.ca/cets
DIMDI – German Institute for Medical Documentation and Information	www.dimdi.de
National Information Center of Health Services Research and Health Care Technology (USA)	http://www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (Finland)	http://www.stakes.fi/finohta/linkit/
Institute of Medical Technology Assessment (Netherlands)	http://www.bmg.eur.nL/imta/
Agencia de Evaluación de Tecnologías Sanitarias (Spain)	http://www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Santé (France)	www.anaes.fr
National Coordinating Centre for Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Health Services Utilization and Research Commission (Canada)	www.hsurc.sk.ca
Centre for Health Program Evaluation (Australia)	http://chpe.buseco.monash.edu.au

Search results

A total of 4078 citations were retrieved from the literature search. The eligibility criteria and results for each of the indications are outlined in each of the subsequent sections on Paget's disease of bone, renal osteodystrophy, prostate cancer and osteoporosis.

Issues in evaluating Ostase

Evaluation of diagnostic tests

Several authors have discussed the sequence of evaluations that can be carried out for a diagnostic test (Gallagher 1993; Jaeschke, Guyatt, & Sackett 1994; National Health and Medical Research Council 2000). These include diagnostic test performance, therapeutic impact and outcome.

- *Diagnostic test performance* ('accuracy') can be measured as sensitivity, specificity or likelihood ratios. This involves comparing test results against a valid reference or 'gold standard' which represents the 'truth'. Appropriate gold standards can include pathology findings (eg, histopathological confirmation of the presence or absence of disease) or clinical outcomes (eg, subsequent disease progression or resolution of symptoms and signs). Ideally, diagnostic test performance is evaluated by cross-

sectional analytical studies (NHMRC Level IV) in which there is an independent blind comparison in an appropriate spectrum of consecutive participants who have undergone both the diagnostic test and the reference standard.

- *Therapeutic impact* is measured as the change in treatment decision made by clinicians in response to the information provided by the test. This can be assessed by comparing the therapeutic impact in patients receiving the test with the status of patients receiving standard care or placebo in randomised controlled trials (NHMRC Level II). However, as this information is often not available, surrogate measures need to be used to infer the likely outcome of the diagnostic test on patient management.

- *Outcome*: Ideally, it is desirable to know whether people who have the test have better outcomes. This can be assessed by examining randomised trials of the test (NHMRC Level II) and outcomes of subsequent management resulting from the test. However, such information is usually not available, and surrogates have to be used. Changes in outcome may be reasonably inferred from a combination of evidence of improved diagnostic accuracy, evidence of changes in management and evidence of the effective treatment of a given condition. That is, in conjunction with evidence of improved diagnostic accuracy and changes in management, there should be evidence (ideally from randomised controlled trials) that alternative treatments or managements result in improved long-term health outcomes for patients. For example, if a diagnostic test allowed earlier diagnosis of a condition, evidence that earlier treatment is more effective than delayed treatment is needed to imply that improved outcomes result from the diagnostic test result.

Methodological constraints may prevent some of these studies being done. For example, if it is not possible to measure a reference standard, assessment of diagnostic test performance is not feasible. If an imperfect reference standard is used, then the results of the evaluation will be seriously flawed. Flow diagrams showing the suggested pathway by which testing should improve outcomes are a helpful way of summarising why we expect that a test may be valuable. Studies carried out for each step or for groups of steps can be appraised and the quality of the evidence can be noted. Flow diagrams can also be helpful in clarifying the specific clinical question of interest. For example, if there are trials showing the effect of testing on the final outcome, studies on the intervening steps are of less interest. Assessing diagnostic accuracy is most relevant when randomised controlled trials suggest that intervention based on that diagnosis is effective.

Measurement of surrogates

A surrogate endpoint is one that is measured in place of the biologically definitive or clinically meaningful endpoint. Typically a definitive endpoint measures clinical benefit, whereas a surrogate endpoint is one that tracks the progress or extent of the disease (Piantadosi 1997). Bone alkaline phosphate, as measured by Ostase, is an example of a surrogate measure. While BALP provides information on bone formation, it does not provide information on health outcomes such as morbidity, mortality or quality of life.

One of the major difficulties in using surrogates regards their validity or strength of association with the definitive clinical outcomes. Thus, it is difficult to draw conclusions concerning health outcomes when only information on surrogate endpoints is provided. This needs to be remembered when reviewing the evidence in this report.

Study quality

Studies vary in quality, whether they are looking at diagnostic accuracy (for which the ideal is cross-sectional analytic studies of consecutive patients all followed up with a valid reference standard) or effect on outcomes (where the ideal is a randomised trial of alternative tests). Study quality influences the reliability and validity of the results of the study. Several checklists of study quality criteria are available, including the NHMRC handbook on how to conduct systematic reviews (National Health and Medical Research Council 2000). Glasziou et al (2002) indicate that to evaluate whether the results reported in an article about diagnostic tests are valid, the issues shown in Table 8 should be considered.

One of the major biases seen in studies of diagnostic tests is verification or 'work-up' bias, in which the result of the test being evaluated influences the decision to perform the reference standard (Begg & Greenes 1983; Choi 1992; Shuchleib et al 1999). A potential example in the current review would be whether patients suspected of having a metabolic bone disease as a result of having a positive test result are more likely to undergo further investigation in order to determine the presence of bone pathology results (the reference standard) than those with a negative test.

Table 8 Evaluating and applying the results of studies of diagnostic tests

Criterion A	Was the test compared with a valid gold reference standard?
Criterion B	Were the test and reference standard measured independently?
Criterion C (verification bias)	Was the choice of patients who were assessed by the reference standard independent of test results?
Criterion D	Was the test measured independently of all other clinical information?
Criterion E	If tests were compared were they either assessed independently of each other on the same patient or done in randomly allocated patients?
Criterion F	If the reference standard occurs later that the test aims to predict, was intervention blind to the test results?

Source: Adapted from Glasziou et al (2002).

Incremental or replacement test?

In clinical practice Ostase may be used as an incremental test, in addition to conventional work-up diagnostic procedures (eg, other blood tests, clinical examination), or as a replacement test for one or more of these procedures.

Ideally, in the situation where Ostase is seen as a replacement test (eg, for TALP), in the monitoring of therapy in Paget's disease, the results of one test should be evaluated blind to the results of the other, to minimise test-review bias. In clinical practice the results of a particular diagnostic test may also be used to provide incremental information over and above that provided by conventional assessment. In this situation, the blinded assessment of test results is not as critical, as it will be used in conjunction with, rather than instead of, other tests in clinical practice.

Whether Ostase is used as a replacement or as an additional diagnostic procedure will also have implications for the cost. Where Ostase is used as an incremental test, any cost offsets resulting from Ostase would relate to changes in management, rather than avoiding the use of other tests.

NHMRC Levels of Evidence

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000). These dimensions (Table 9) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 9 NHMRC dimensions of evidence

Type of evidence (domain)	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *P*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 10.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 10. Note, however, that this primarily relates to studies examining a therapeutic intervention and is not applicable to diagnostic tests. As already mentioned, a cross-sectional analytic study of consecutive patients (NHMRC Level IV) is the ideal study type when evaluating diagnostic accuracy, and a randomised trial of alternative tests (NHMRC Level II) is most relevant when looking at the effect of a test on health outcomes.

Table 10 Designation of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC, 1999.

Results of assessment

Performance characteristics of Ostase tests

This section details the performance characteristics of Tandem-R Ostase, Tandem-MP Ostase and Access Ostase. In order to assess whether each Ostase should be evaluated separately or in combination, it is important to determine the degree of agreement between the tests. Furthermore, as Ostase is a potential replacement test for electrophoresis (the current method funded under the MBS), it is necessary to establish whether the test results are correlated between Ostase tests and electrophoresis. Therefore, this section assesses the degree of agreement in the determination of BALP among Tandem-R, Tandem-MP and Access Ostase tests, and between the Ostase tests and electrophoresis.

Papers that measure serum BALP by another method such as wheat germ lectin precipitation and HPLC have been excluded, as these methods are not frequently used in Australia and are not currently listed on the MBS. Note that while the following papers were identified during the eligibility process, they were not specifically identified through a systematic evaluation of the literature.

Results

Seven papers were retrieved for inclusion in this section. The performance characteristics for Tandem-R and Tandem-MP Ostase are summarised in Table 11. No full peer-reviewed papers were retrieved that assessed the Access Ostase test. Information relating to Access Ostase is reported in a recently published abstract from the American Association of Clinical Chemistry and available from a United States FDA report (2000).

Table 11 Performance characteristics of Ostase tests that determine the specific mass measurement of bone alkaline phosphatase (BALP) in the serum of patients with Paget's disease of bone

Study	*n*	Imprecision (% coefficient of variation)		Degree of cross-reactivity with liver isoenzymes or analytical specificity	Detection limit (µg/L)	Agreement between Ostase test and electrophoresis	Agreement among Ostase tests
		Inter-assay precision	Intra-assay precision				
Tandem-R Ostase							
Garnero et al (1993)	57	<9%	<7%	16%	0.2	r^2 = 0.92 (P < 0.001)	–
Panigrahi et al (1994)	100	6.7% – low	4.5% – low	14.7%	0.4	r^2 = 0.929[b]	–
		7.4% – med.	3.5% – med.				
		5.9% – high[a]	5.9% – high[a]				
Price et al (1995)	95	3.9%–9.8%	5.4%–11.8%	16.5%–18.3%	0.34	r^2 = 0.70 (liver patients)	–
	53					r^2 = 0.86 (healthy children)	
	96					r^2 = 0.98 (Paget's patients)	
Van Hoof et al (1995) & Martin et al (1997)	79 & 214	–	< 5%	–	–	r = 0.92	–
Rauch et al (1997)	128	–	–	–	–	r = 0.87 to 0.91	r = 0.87–0.91[c]
Tandem-MP Ostase							
Broyles et al (1998)	251	2.3%–3.9%	2.7%–6.1%	16.2% (Tandem-MP)[d] 16.7% (Tandem-R)[d] 8.1% (Tandem-MP)[e] 8.3% (Tandem-R)[e]	0.61 ± 0.18 (0.26–0.90)	–	r = 0.97
Access Ostase							
Kress et al (1999b)	140	3.3%–5.9%	1.5%–2.6%	10%	<0.1	–	r = 0.9895

[a] The coefficients of variation were reported for low-, medium- and high-concentration serum control pools.
[b] Regression analysis revealed the following relationship: Tandem-R = 0.3540 electrophoresis + 20.5.
[c] These results are the range for electrophoresis, Tandem-R Ostase and Alkphase B.
[d] Determined by 'slope comparison' method.
[e] Determined by heat inactivation.

Tandem-R Ostase

Garnero et al (1993) evaluated the degree of agreement between Tandem-R Ostase and electrophoresis in the determination of BALP in the serum of patients with Paget's disease of bone and reported a significant relationship (Table 11).

Panigrahi et al (1994) also evaluated the agreement between Tandem-R Ostase and electrophoresis in patients with Paget's disease. The regression relationship was:

$$\text{Tandem-R Ostase} = 0.3540 \text{ electrophoresis} + 20.5,\ r^2 = 0.929.$$

Price et al (1995) compared the performance of Tandem-R Ostase and electrophoresis in detecting BALP in sera from patients with liver disease, patients with Paget's disease of bone and children with no history of bone disease (Table 11). The relationship between the two tests was weakest in patients with liver disease ($r^2 = 0.70$), indicating that more results were discordant.

Van Hoof et al (1995) and Martin et al (1997) both compared the performance of agarose electrophoresis and Tandem-R Ostase in detecting BALP in 79 patients with

end-stage renal failure and 214 patients with malignant disease. They found that while the overall correlation between the two methods was good (r^2 = 0.92), the correlation was lower for low values of BALP and in a number of samples with high total LALP activity. They found that while a BALP concentration of ≤ 5 μg/L measured by electrophoresis indicated low osteoblastic activity, a normal or even high BALP concentration as determined by Tandem-R Ostase would not confirm osteoblastic activity. The reason for this was thought to be related to the cross-reactivity of the anti-BALP antibodies of the Ostase kit with LALP. Omitting samples with higher LALP improved the correlation between the two methods to 0.97.

Rauch et al (1997) compared the performance of electrophoresis, Tandem-R-Ostase and Alkphase B in detecting BALP. Consecutive samples were obtained from 128 children and adolescents with various illnesses, including chronic renal failure. Little information was reported, but the authors noted that the mean intra-assay coefficient of variation for electrophoresis was 4.3 per cent, and the intra-assay variability for Tandem-R-Ostase was 6.3 per cent. They also noted that correlation coefficients among BALP assays ranged from 0.87 to 0.91, and concluded that Tandem-R-Ostase and Alkphase B did not have a detectable advantage over lectin affinity electrophoresis in the determination of BALP in children.

The detection limits reported in these studies varied between 0.2 and 0.4 μg/L, which is lower than the reference intervals for normal adults. The reference intervals from the Central Sydney Laboratory Service are 3.7–20.9 μg/L for males, 2.9–14.5 μg/L for premenopausal women and 3.8–22.6 μg/L for post-menopausal women.

Tandem-MP Ostase

Broyles et al (1998) compared the analytical and clinical performances of Tandem-MP Ostase and Tandem-R Ostase. Reference ranges were established in 200 apparently healthy ambulatory men and women. BALP concentrations determined by the Tandem-MP Ostase and Tandem-R Ostase assays showed no statistical differences (Table 11). Mean ± SD values were 13.2 ± 5.9 μg/L and 12.2 ± 4.4 μg/L respectively. The methods were also compared in 285 serum samples obtained from apparently healthy premenopausal (n = 73) and postmenopausal (n = 75) women, men (n = 52) and patients with Paget's disease of bone (n = 51). The following regression relationship between the two Ostase methods was reported:

Tandem-MP Ostase = 1.03 Tandem-R Ostase + 0.22 μg/L

($S_{y/x}$ = 4.0 μg/L, r = 0.97).

The reactivity of Tandem-MP Ostase and Tandem-R Ostase with liver alkaline phosphatase (LALP) was determined by two methods: slope comparison and sample heat inactivation. The degree of cross-reactivity was lower by the heat inactivation method (Table 11). The detection limit falls below the reference interval for normal adults (see previous section).

Access Ostase

A United States FDA report (2000) investigated the safety and effectiveness of Access Ostase, and indicated that it was substantially equivalent to Tandem-R Ostase. Kress et al (1999b) also provide information about the Access Ostase test in a recently published abstract from the American Association of Clinical Chemistry meeting in 1999. The

authors report that regression analysis (n = 140) revealed the following conversion equation:

Access Ostase = 0.96 (Tandem-R Ostase) + 1.0 μg/L

($S_{y/x}$ = 5.4 μg/L, r = 0.9895).

Kress et al (1999b) reported that the Access Ostase dynamic range is 120 μg/L with a detection limit of <0.1 μg/L, which falls below the reference interval for normal adults. The reactivity with human serum LALP is comparable with values for Tandem-R Ostase and Alkphase B (Table 11).

Conclusions

- In the determination of serum BALP levels, a reasonably strong correlation was reported both among Ostase tests and between the Ostase test and electrophoresis.
- A cross-reactivity of about 10 per cent occurs with alkaline phosphatase of liver origin. This may limit the utility of this test in patients with significant elevations of LALP.
- Within- and between-run precision appear satisfactory for clinical use.
- The limit of quantitation of the assay allows quantitation of BALP down to levels below those found in healthy persons.
- No information on the sensitivity and specificity of the Ostase tests compared with each other or with electrophoresis was reported.

Assessment of the clinical utility of Ostase

Is it safe?

Ostase is an *in vitro* diagnostic laboratory test that measures BALP in human sera. As such, there is no safety risk to patients. Laboratory staff and organisations intending to use the Ostase laboratory kit should ensure the safe handling of blood and other fluids as outlined in the health and safety guidelines of the National Pathology Accreditation Advisory Council (2002).

Is it effective?

The questions pertaining to possible utility of Ostase in the detection of bone turnover in Paget's disease of bone, renal osteodystrophy, prostate cancer and osteoporosis are addressed separately in the subsequent sections.

Paget's disease of bone (osteitis deformans)

The clinical problem

The following review assesses the role and value of Ostase in relation to Paget's disease of bone. Specifically, the following clinical questions will be addressed:

- What is the additional value of Ostase to TALP in the diagnosis of Paget's disease of bone in patients suspected to have the condition?

- What is the value of Ostase compared with TALP in the monitoring of patients who have undergone pharmacological treatment for Paget's disease of bone?

The clinical management of Paget's disease of bone has changed in recent years. Traditionally, only symptomatic patients with active disease received treatment. However, with the advent of more effective drug therapies, asymptomatic patients may now be eligible to receive treatment to prevent the progression of the disease. These patients may include people who are diagnosed with the disease at a younger age and/or present with disease at sites likely to be associated with complications, such as joint degeneration and nerve compression (Meunier & Vignot 1995; Siris 1999a; Siris 1999b). Two markers of bone metabolism, serum TALP and urine hydroxyproline (Hyp), have been extensively used to assist in the diagnosis and treatment monitoring of Paget's disease. However, as serum TALP may not be highly elevated in these new patient groups, its measurement may not detect small changes in bone metabolism. Ostase specifically measures the bone isoenzyme of TALP (BALP) in the blood and may therefore be a more sensitive test of bone metabolism in Paget's disease, particularly in patients in whom disease activity is low (Eastell 1999).

Epidemiology and clinical presentation

Paget's disease of bone primarily occurs among Caucasians in Europe, North America, New Zealand and Australia, and is less common in Asia and Africa (Kanis 1998; Malcolm 2002). The disease is thought to be initiated by a viral infection in susceptible people, but the causal link between viral infection and the development of the disease is not clearly understood (Kanis 1998; Reddy, Singer, & Roodman 1995). It is difficult to determine the prevalence of Paget's disease in the population, because many people have asymptomatic disease. Following a review of the literature, Kanis (Kanis 1998) suggests that approximately 3 to 4 per cent of people over 40 years may have this condition. Paget's disease of bone generally becomes clinically evident after the fourth decade, and is more prevalent with increasing age (Kanis 1998). There is, however, some evidence to suggest that in more recent years, there has been a decline in both the incidence of Paget's disease and the severity of the disorder (Cooper et al 1999).

It is characterised by abnormal bone remodelling leading to initially lytic areas followed by the development of new sclerotic bone that is deformable despite its density, owing to abnormal architecture. The bone affected is not structurally sound and therefore is more susceptible to fractures and deformation when placed under biomechanical stress (Coutran, Kumar, & Robbins 1989; Kanis 1998).

Paget's disease of bone generally presents as polyostotic disease affecting multiple bones, commonly the pelvis, lumbar vertebrae and femur. Monostotic disease is reported less frequently, possibly affecting 10 to 20 per cent of symptomatic patients. The pattern of disease differs from polyostotic disease, commonly affecting the ilium, tibia and femur. Other sites may be also be affected by Paget's disease, including the humerus, skull and sacrum (Kanis 1998).

When symptoms do occur they are highly variable and dependent on the severity of disease, whether it is monostotic or polyostotic and the extent to which adjacent anatomical structures are affected. All bones affected by Paget's disease are susceptible to pathologic fractures. Fractures and enlargement of bone can cause pain, deformity and nerve compression when adjacent to nerve structures. Anterior bowing of the tibia and femur can cause altered mechanical stress on the knee, foot, hip and spine due to limb length discrepancy, thus increasing the likelihood of osteoarthritis in these joints. Enlargement of vertebrae or compression fractures of the spine can lead to spinal curvature, osteoarthritis, nerve root compression, pain and paraplegia. Hearing loss may occur when the eighth cranial nerve is compressed by thickening skull bone (Coutran, Kumar, & Robbins 1989; Kanis 1998).

As a result of increased bone marrow vasculature, the skin overlying the affected bone may be warm to touch. In polyostotic disease, increased vascularity at numerous sites can cause increased cardiac output, leading to subsequent cardiac disease and heart failure, but this is a rare complication. In a small number of patients, bone cancer or osteosarcoma can also arise. Tumours are more likely to affect the jaw, pelvis or femur, and tend to be more aggressive than osteosarcomas arising in the absence of Paget's disease of bone (Coutran, Kumar, & Robbins 1989; Kanis 1998).

Conventional diagnosis and treatment

Diagnosis and stages of disease

The extent of disease is generally diagnosed and evaluated by nuclear medicine techniques. Bone scans and X-rays are able to provide information on the extent to which adjacent structures, such as joints and nerves, are affected by the disease process. Biochemical markers such as serum TALP also reflect disease activity and are used in the diagnostic work-up. Very high TALP levels almost always indicate Paget's disease. However, it is thought that approximately 10 per cent of patients with symptomatic disease have normal TALP levels, and therefore low or normal TALP levels should not be used to exclude the diagnosis of Paget's disease (Kanis 1998).

Paget's disease is characterised by various disease stages of abnormal levels of bone resorption and formation, including increased activity of osteoclasts leading to the resorption of bone, followed by the production of less structurally sound woven bone associated with increased bone vascularity. A reduction of bone vascularity can follow and is associated with the formation of dense, sclerotic, poorly organised bone. Note that although these phases have been identified through biochemical and radiological evaluation, they are still not clearly defined and can occur concurrently (Kanis 1998).

Treatment

Currently, there is no cure for Paget's disease of bone. The principle aim of treatment is to suppress disease activity to a level that prevents the onset of further complications. In

Australia, the potent bisphosphonates are the primary drugs prescribed for the treatment and management of Paget's disease of bone, and are currently funded under the Pharmaceutical Benefits Scheme (PBS). These drugs have been shown to act directly on the disease process, effectively suppressing abnormal bone turnover in patients with Paget's disease. Surgery, physical therapy and the prescription of other analgesics may also be used in conjunction with these treatments.

Calcitonins were previously prescribed before the development of the more effective bisphosphonates. Calcitonins reduce osteoclastic bone resorption and improve normal bone turnover. If used for a prolonged period of time, these drugs increase skeletal mass and prevent disease progression by facilitating the deposition of lamellar rather than woven bone and reducing bone vascularity. The drugs are administered parenterally via subcutaneous or intramuscular injection. Adverse events commonly associated with the administration of calcitonin include nausea, flushing, vomiting, diarrhoea, pain at injection site and transient increases in vascularity at the extremities (Kanis 1998).

Bisphosphonates, including tiludronate, alendronate, risedronate and intravenous pamidronate, also inhibit osteoclast-mediated bone resorption. In the early 1990s more potent bisphosphonates became available for the treatment of Paget's disease of bone, and now are regarded as first line therapy. Tiludronate, alendronate, risedronate and intravenous pamidronate are currently funded under the PBS for the treatment of Paget's disease of bone. These drugs appear to more effectively suppress abnormal bone turnover than older bisphosphonates like etidronate (Drake, Kendler, & Brown 2001; Kanis 1998). Bisphosphonates can be administrated either orally or parenterally. Treatment is usually prescribed for a period of 2 to 6 months. Following treatment, patients are monitored and may receive another course if the disease relapses. Gastrointestinal upset is the most common adverse event associated with bisphosphonates when they are administered orally, and musculoskeletal pain can occur occasionally following intravenous administration (MIMS Australia 2003).

Although biopsy and radiographic evaluation following bisphosphonate therapy suggests that normalisation of bone turnover results in new bone deposition, further research from large, long-term prospective studies are required to assess whether these effects translate to a reduction in the incidence of clinical complications, such as deformity and fracture. Comparative studies are also needed to evaluate the relative effectiveness of different drug regimes on these long-term clinical end-points (Drake, Kendler, & Brown 2001; Kanis 1998; Siris 1999a). The Paget's disease: a Randomised trial of Intensive vs Symptomatic Management (PRISM), currently being conducted in the United Kingdom, may provide long-term health outcome data. This study aims to investigate whether intensive pharmaceutical treatment with potent bisphosphonates (risedronate or pamidronate) compared with conventional symptomatic treatment reduces the incidence of long-term health outcomes in patients with Paget's disease. The study aims to enrol 1700 patients and follow the groups for 3 years.

Other treatments such as non-steroidal anti-inflammatory drugs, physical therapy and orthoses can also be prescribed to provide additional pain relief and maintain function. Surgical interventions are also often required in the management of fractures, osteoarthritis and nerve compression (Kanis 1998).

Treatment monitoring

Biochemical markers such as TALP are commonly used to monitor the effects of calcitonin and bisphosphonates on bone metabolism. Changes may also be monitored with radiography, bone scans and histology. However, as these techniques can be costly and more invasive and often expose the patient to radiation, it is not feasible to use these in routine clinical monitoring.

In the absence of liver disease, serum TALP levels have been shown to closely reflect osteoblastic activity. In patients with Paget's disease of bone, serum TALP may be highly elevated, particularly when polyostotic disease is present (Broyles et al 1998; Price et al 1995). Moreover, serum TALP levels tend to decrease in response to the administration of bisphosphonates (Broyles et al 1998). Previously, a 25 per cent change in TALP following treatment was considered to indicate a response or relapse, but normalisation of biochemistry levels is now used as the primary end-point in treatment monitoring, and the degree of suppression can indicate the period of remission. X-ray resolution of lytic changes can also be used in treatment monitoring. In a small percentage of patients who present with reduced disease activity (such as in monostotic Paget's disease), serum TALP may not be significantly elevated, precluding its usefulness for treatment monitoring in these patients (Kanis 1998). Moreover, in the presence of concomitant liver disease, it may be difficult to interpret TALP measures, as it is not possible to delineate the relative contributions of liver and bone isoforms.

Determination of treatment effectiveness, however, cannot completely rely on biochemical assessment. The measurement of longer-term clinical outcomes is also necessary in order to assess the effectiveness of treatment in the reduction of the incidence of fracture, nerve compression, osteoarthritis and other complications associated with Paget's disease of bone.

Potential value of Ostase

This review examines the potential role of Ostase in assisting in the diagnosis of Paget's disease of bone, and determining treatment response in patients with Paget's disease of bone. These roles are illustrated in the clinical flow chart in Appendix F.

Preliminary results from some studies have indicated that BALP as measured with Ostase appears to reflect disease status in patients with Paget's disease. Alvarez et al (1997) found that in a series of 51 patients with Paget's disease, a range a biochemical markers, including BALP measured with Tandem-R Ostase, were significantly correlated with semiquantitative scintigraphic indices. Mean values for both BALP and TALP were also significantly elevated in patients with Paget's disease compared with controls, and in patients with polyostotic disease compared with patients with monostotic disease. Another study by Alvarez et al (2000) showed that BALP had low biological variability in patients with stable Paget's disease followed for 1 year, indicating that BALP may be sensitive in detecting early change in disease activity. This hypothesis was tested in a subsequent study by the authors (Alvarez et al 2001), who evaluated the response of a range of biochemical markers, including BALP, in 38 patients with Paget's disease following treatment with oral tiludronate (400 mg/day). The authors reported that even when accounting for biological variability, BALP levels showed >60 per cent reduction. Although this response is significantly greater than in TALP ($P < 0.001$), the authors still advocate the usefulness of TALP in monitoring treatment response in the majority of patients, claiming that it may be a more cost-effective option.

Serum TALP, however, may be less useful in the diagnosis or treatment monitoring of Paget's disease in patients with either low-activity disease or monostotic disease, or in patients with concurrent liver disease, as in these patient groups TALP will be less sensitive to changes in the disease process (Kanis 1998). BALP, the bone isoform of TALP, may be a more sensitive measure in such patient groups, assisting in diagnosis and treatment monitoring.

Furthermore, if BALP is a more sensitive measure of treatment response, it may have the potential to more accurately determine whether bone turnover is effectively reduced by drug treatments, therefore assisting in clinical decision-making regarding choice of drug regimes. However, until the results become available from current, long-term, prospective clinical trials assessing the impact of different drug regimes on health outcomes such as incidence of fracture, skeletal deformity and joint and neurological pathology, it is difficult to determine whether a change in therapy driven by Ostase results would lead to an improvement in patient outcomes.

Review of the literature

Search strategy

The search strategies used to identify relevant studies for Paget's disease are outlined in the Approach to Assessment section (page 7).

Eligibility criteria

The eligibility criteria used to evaluate abstracts and full papers are shown in Table 12. These criteria relate to the study question as summarised in Appendix E.

Table 12 Eligibility criteria for Paget's disease of bone

Patients	Patients had Paget's disease of bone, including: newly diagnosed, untreated treated patients undergoing follow-up patients with low TALP values.
Intervention	Papers had to measure BALP by Tandem-R-Ostase, Tandem MP Ostase or Access Ostase. Papers in which BALP was measured by Alkphase B or by electrophoresis were excluded.
Comparator	Serum total alkaline phosphatase (TALP)
Other	The outcome measure had to be relevant to the study question. Papers were excluded if fewer than 10 patients were reported on. The exception to this may be in the situation where there are no publications with more than 10 patients. Rather than excluding all papers for a clinical indication on the basis of this criterion, available information is reported, noting limitations. Review-only / editorial / technical papers were excluded. Data available in abstract form only were excluded. All non-English papers were excluded. Papers which report no clinical results were excluded.

Results

The search of databases and Web sites of international health technology assessment agencies did not identify any relevant health technology assessments for this indication.

The search of electronic databases identified 339 non-duplicate citations relating to Paget's disease of bone.

Two hundred and eighty-seven studies (294 citations) were excluded on the basis of these eligibility criteria.

Eighteen studies were excluded on the basis of patient group, 128 on intervention and 141 on other criteria.

An additional 13 studies were not excluded in this process, but were used as background papers for various aspects of the review.

A further 50 of these studies were excluded because they did not measure BALP using Ostase or did not report diagnostic accuracy.

Thirty-two papers were then examined in more detail, as it was not possible to determine their eligibility from abstracts. A further 30 studies were excluded because they did not measure BALP using Ostase or did not report diagnostic accuracy.

Two studies thus form the basis of this review and are summarised in Table 46 in Appendix C. Table 13 outlines the number of studies that address each respective research question for Paget's disease of bone.

Table 13 Publications on Paget's disease of bone

Clinical question, name of paper	NHMRC Level	Number
Diagnosis		2
Alvarez et al (1995)	Level IV	
Woitge (1996)	Level IV	
Treatment monitoring		0
Total		**2**

Methodological issues in the studies

As outlined in Appendix G, several factors may compromise a study's validity, and therefore limit the extent to which the results can be generalised to clinical scenarios.

The two case-series that form the basis of this review were of generally poor methodological quality. The following methodological issues limited the extent to which the data reported by these studies could be evaluated:

- There was some variation between the studies as to the cut-off points used for BALP and TALP.
- Sample groups did not represent consecutive series. It is difficult to determine the extent to which patient selection affected the study results.
- Patients with other metabolic diseases (eg, arthritis) and liver or renal disease were excluded from study samples. This will limit the extent to which results can be generalised to clinical populations.

Diagnostic accuracy of Ostase

Diagnosis

Alvarez et al (1995) investigated the usefulness of a range of markers of bone metabolism in the diagnosis of patients (n = 59) with Paget's disease of bone. BALP was reported to have a sensitivity of 84 per cent when the specificity was set at 100 per cent, and TALP had a sensitivity of 78 per cent. The sensitivity of TALP was reduced, as nine patients with normal TALP had elevated BALP values. There is insufficient data to determine values for other diagnostic measures. The authors report that when TALP is low, BALP may be a more sensitive marker in detecting Paget's disease of bone.

Woitge (1996) investigated the usefulness of BALP compared with TALP in the diagnosis of a number of conditions affecting bone metabolism. The study comprised a consecutive series of 355 participants stratified into three major groups: (i) healthy adults (n = 119), (ii) hospitalised patients with non-skeletal diseases (n = 123), and (iii) hospitalised patients with metabolic bone disease (n = 113). Diagnosis of Paget's disease of bone was confirmed in 26 of the patients with metabolic bone disease. For the diagnosis of Paget's disease of bone, receiver operator characteristic (ROC) curve analysis indicated that the areas under the curve for TALP and BALP were 0.945 and 0.979, respectively. Sensitivity was assessed by calculating the percentage of patients with Paget's disease of bone whose results were above the upper limit of normal (ULN) of the healthy control group. Diagnostic accuracy was calculated separately for postmenopausal women and male Paget's disease subgroups. Values of sensitivity were comparable for both BALP and TALP: (i) 83 per cent in postmenopausal women, where ULN for BALP was 20.2 ng/mL and TALP was 171.2 U/L; and (ii) 100 per cent for men, where ULN for BALP was 18.0 ng/mL and TALP was 181.5 U/L. There is insufficient data to determine values for other diagnostic measures. It should be highlighted that the concordance between the TALP values and the diagnosis of Paget's disease may have been artificially inflated because TALP values were used as part of the diagnostic work-up for determining Paget's disease, and therefore it is possible that the results from this study may underestimate the diagnostic accuracy of BALP in diagnosing Paget's disease. Furthermore, all the patients in this study had active disease with high TALP values, and therefore may not represent the clinical population in which BALP might be most useful.

Treatment monitoring

Little is reported on in relation to the role of BALP, as measured by Ostase, in the monitoring of treatment in patients with Paget's disease of bone. One study indicated that BALP, as measured with Ostase, is significantly reduced after treatment with bisphosphonate therapy (de la Piedra et al 1996). Another study found that BALP may be better at detecting change in bone turnover after bisphosphonate treatment than TALP (Alvarez et al 2001). However, these studies enrolled small samples and do not give any indication as to the accuracy of BALP. Further research is required in this area to further define the role of BALP in the monitoring of Paget's disease of bone.

Impact of Ostase on clinical management

No specific information regarding therapeutic impact of Ostase on clinical management of Paget's disease of bone was identified in the search conducted for this review. It is possible, however, that Ostase may play a role in determining optimal treatment options

by detecting low-activity disease in patients with Paget's disease of bone or provide more accurate information in treatment monitoring. Further evidence evaluating how Ostase compares with TALP facilitates changes in decisions regarding treatment is still required.

Impact of Ostase on patient outcomes

No studies were identified that reported on the impact of BALP, as measured by Ostase, on patient outcomes. Although many studies have investigated the impact of pharmacological treatments on biochemical markers, few have determined the effect of treatment on health outcomes, such as pain, mobility and quality of life. The measurement of health outcomes in patients with Paget's disease of bone is inherently difficult, given that the disease may affect a variety of physiological and psychological factors. It may be that Ostase could result in improved health outcomes, but until evidence from ongoing trials such as the PRISM study become available that evaluate the effectiveness of interventions for Paget's disease on health outcomes, it is difficult at this stage to draw any conclusions. Long-term prospective studies are required to ascertain the role of Ostase in the improvement of health outcomes in patients with Paget's disease of bone.

Conclusions

- The conclusions regarding the diagnostic accuracy of BALP in the diagnosis of Paget's disease of bone are based on a very small amount of evidence.
- Although some studies suggest that Ostase is a more sensitive marker of bone turnover than TALP, and therefore may assist in the diagnosis of Paget's disease of bone, there is currently insufficient evidence at this time to draw any definitive conclusions.
- There is limited evidence at this time to indicate the role of Ostase in the monitoring of treatment responses in patients with Paget's disease of bone. Further evaluation is required.
- There is currently insufficient evidence to indicate the role of Ostase in improving health outcomes and altering management of patients with Paget's disease of bone.

Renal osteodystrophy

The clinical problem

The following review assesses the role and value of Ostase in relation to renal osteodystrophy. Specifically, the following clinical questions are addressed:

- What is the additional value of Ostase to other biochemical measures in the diagnosis and differentiation of the different patterns of bone disease in patients with prolonged low renal function (GFR < 30 mL/min)?

- What is the additional value of Ostase to other biochemical measures in the monitoring of treatment in patients with renal osteodystrophy?

The review also summarises additional information on other potential roles of Ostase in the assessment of renal osteodystrophy, where appropriate.

Epidemiology and clinical presentation

In patients with renal impairment, bone disease is relatively common: 75 to 100 per cent of patients with a glomerular filtration rate (GFR) below 60 mL/min are reported to have metabolic bone disease (Elder 2002). Renal osteodystrophy describes a variety of metabolic bone disorders that occur as complications of impaired renal function, and is associated with significant complications and long-term morbidity. There are several different forms of osteodystrophy, the dominant variants being osteitis fibrosa cystica, or hyperparathyroid bone disease, and osteomalacia, although a mixture of the two patterns is found in many patients. Adynamic bone disease is less common. Additionally, variants may be classified (Table 14) on the basis of the rate of bone turnover as:

- high-turnover bone disease (HTBD), characterised by an excess of parathyroid hormone (PTH) secretion

- low-turnover bone disease (LTBD), which is most commonly associated with normal or reduced serum PTH levels.

Note that renal osteodystrophy is not a static phenomenon, as transformation occurs between forms (Elder 2002).

Table 14 Classification of renal osteodystrophy in patients with impaired renal function

High-turnover bone disease	Low-turnover bone disease
Secondary hyperparathyroidism (osteitis fibrosa)	Adynamic bone disease
Mild disease	Osteomalacia
Mixed lesion	Mixed lesion

The prevalence of the variants has changed over the last 15 years. There has been a decrease in the occurrence of osteomalacia and mixed osteodystrophy, while adynamic bone disease has become more common. Little information is available, however, on the

prevalence of renal osteodystrophy either in Australia or internationally. Prevalence figures have primarily been gleaned from clinical studies, and therefore it is difficult to generalise these findings to the wider population. A summary of the literature on biopsy-proven prevalence rates of the different forms of renal osteodystrophy is presented in Table 15.

Table 15 Prevalence of renal bone disease in predialysis patients

Reference	GFR	*n*	Sex	Histology				
	mL/min		(M/F)	Normal	OF/HPT	Mixed	OM	ABD
Hamdy et al (1995)	15–50	176	107/69	25%	55%	14%	1%	5%
Lafage et al (1992)	< 20	17	14/3	23%	53%	24%	0%	0%
Hutchison et al (1993)	Pre-CAPD	30	23/7	0%	50%	13%	7%	27%
Bianchi et al (1994)	48 ± 12	17	8/9	0%	29%	53%	18%	0%
Torres et al (1995)	Pre-dialysis	38	23/15	0%	40%	10%	2%	48%
Coen et al (1996)	19–54	76	44/32	13%	3%	63%	9%	12%
Hernandez et al (1994)	< 10	92	61/31	0%	56%	0%	11%	33%

Abbreviations: ABD, adynamic bone disease; CAPD, continuous ambulatory peritoneal dialysis; OF/HPT, osteitis fibrosa / hyperparathyroidism; OM, osteomalacia.
Source: Adapted from Elder (2002).

Types of renal osteodystrophy

It is important to differentiate between the variants of renal osteodystrophy, because treatment differs for each form of the disease. A brief description of each form of renal osteodystrophy is outlined in Table 16 and Table 17.

Table 16 Different forms of renal osteodystrophy

Types of renal osteodystrophy	
Secondary hyperparathyroidism (osteitis fibrosa)	The classic histologic form of renal osteodystrophy is osteitis fibrosa and represents the response of bone to persistently elevated levels of PTH (Osella et al 1997). This excess of PTH leads to an increase in the activation frequency and consequently to a marked increase in bone turnover. Changes include an increase in the number and size of osteoclasts and osteoblasts (Malluche & Faugere 1990). Collagen production is also elevated, resulting in an increase in osteoid surface and volume. The disease is observed in approximately 5% to 50% of patients and appears to be decreasing, primarily as a result of better suppressive treatment of PTH hypersecretion.
Mild lesion	In patients with mild lesion, PTH levels are increased but lower than in patients with secondary HPT. Similarly, osteoclastic and osteoblastic activities are also elevated but are not as pronounced as in osteitis fibrosa. Peritrabecular fibrosis is absent in mild lesion. This lesion is most commonly seen in patients before the development of end-stage renal disease and is increasing in frequency in patients on dialysis (Ho 2002).
Mixed osteodystrophy	This form of renal bone disease has histological features of both osteitis fibrosa and osteomalacia. It is characterised by an increased fibrosis area as well as increased osteoid volume (Fournier et al 1997). Mixed renal osteodystrophy can be seen in patients with osteitis fibrosa who are in the process of developing aluminium-related bone disease, or in patients with aluminium bone disease in whom therapy has resulted in PTH levels increasing. Therefore, mixed lesion may represent a state of transition between high-turnover and low-turnover renal osteodystrophy (Goodman 2001).
Adynamic bone disease	The pathogenesis of adynamic bone disease is poorly understood (Hruska & Teitelbaum 1995). Adynamic bone disease is a form of renal osteodystrophy characterised by a marked decrease in both remodelling and mineralization (Ho 2002). There is a profound decrease in both osteoblasts and osteoclasts, and low or unmeasurable rates of bone formation. Serum PTH levels are also lower in patients with adynamic bone disease than with other forms of renal osteodystrophy, and it is thought that adynamic bone disease reflects a state of relative hypoparathyroidism. There is also some evidence to suggest that patients with adynamic bone disease have more fractures and an increased mortality rate than patients with other forms of renal osteodystrophy (Hruska & Teitelbaum 1995).
Osteomalacia	Osteomalacia is a disorder characterised by low rates of bone turnover, a mineralisation defect and an accumulation of unmineralised osteoid (bone matrix) (Hruska & Teitelbaum 1995). It is less common than adynamic bone disease, and has a higher prevalence in developed countries (Couttenye et al 1999). Osteomalacia in patients with chronic renal failure can arise from causes such as vitamin D deficiency, severe acidosis or persistent hypocalcaemia and/or hypophosphataemia (Goodman 2001). Aluminium toxicity in the past was also a common cause of osteomalacia in patients undergoing dialysis. However, owing to effective water treatment for haemodialysis and a decreased use of aluminium tablets taken to control phosphate, aluminium-related osteomalacia is now an uncommon finding in patients with chronic renal failure.

Abbreviations: HPT, hyperparathyroidism; PTH, parathyroid hormone.

Table 17 Other forms of bone disease related to renal osteodystrophy

Other related forms of bone disease	
Aluminium bone disease	Aluminium bone disease is not typically defined as a true form of renal osteodystrophy. It is, however, associated with low bone turnover disease. In the majority of cases of aluminium bone disease, patients would be classified as having osteomalacia or adynamic bone disease. The low bone turnover may, however, be attenuated in the presence of HPT (Malluche & Faugere 1990). This has particular relevance as, should a parathyroidectomy be performed, the resultant reduction of PTH in such a patients could contribute to the development of low bone turnover osteomalacia (Felsenfeld & Torres 2001).
Amyloid bone disease	Amyloid bone disease is a condition that can develop in those who have been on dialysis for many years. This is caused by the deposition of a small protein (beta 2 microglobulin) in the soft tissues and bone. The protein is normally excreted by the kidneys. However, it accumulates in dialysis patients because dialysis does not remove it completely. Symptoms of amyloidosis, such as pain, stiffness and swelling around the joints, generally occur after 10 to 15 years of treatment. Improved dialysis membranes and dialysate preparations have been shown to be more efficient in removing the amyloid protein and may also reduce the production of the beta-2-microglobulin. Therefore, it is hoped that these improvements will result in a reduced incidence of this condition. Transplantation, however, is the treatment of choice for dialysis-related amyloidosis. It lowers the blood concentration of beta 2 microglobulin to normal, thus halting the progression of the disease. In fact, symptoms such as joint pain, swelling and stiffness can disappear within the first week after transplantation.
Osteoporosis	Renal bone disease also occurs alongside the more common process of osteoporosis. Although osteoporosis occurs with ageing, it is exacerbated in patients with prolonged renal insufficiency. This is primarily due to alterations in calcium, phosphorus and vitamin D metabolism (Elder 2002). Aluminium and PTH also play a role in this link with BMD and fracture risk. The site of bone loss is highly dependent on the histological type of renal osteodystrophy. For example, aluminium bone disease targets trabecular bone and HPT cortical bone (Fournier et al 2001a).

Clinical signs and symptoms

Patients with renal osteodystrophy are not always symptomatic. Clinical manifestations include fractures, joint pain, proximal myopathy, hypercalcaemic syndrome with nausea, vomiting, confusion or psychological disturbances (Fournier et al 1998). The most common symptom, however, is bone pain, which generally appears in advanced forms of renal osteodystrophy. While bone pain can occur in patients with either high- or low-bone turnover disease, it is most often observed in osteomalacia and aluminium-related adynamic bone disease. In adynamic bone disease without aluminium accumulation, the patient is usually asymptomatic (Fournier et al 2001b).

Children and growing individuals with renal osteodystrophy, however, may present with a different clinical picture (Malluche & Faugere 1990). Although these individuals may still experience bone pain, vascular calcification is infrequent, and children may also present with growth retardation.

Conventional diagnosis and treatment

Diagnosis

The gold standard in determining the classification of renal osteodystrophy and treatment is a bone biopsy, typically performed after double tetracycline labelling. This method can provide precise information on parameters such as bone formation rate, osteoid volume and osteoid thickness, which aid in the diagnosis of the variant and severity of renal osteodystrophy (Coen 1994).

Bone biopsy, however, is considered an invasive and technically difficult procedure (Ho 2002); and, as outlined in the *Caring for Australians with Renal Impairment (CARI) Guidelines* (Australian and New Zealand Society of Nephrology and the Australian Kidney Foundation 2001), bone biopsy is not necessary for beginning or monitoring treatment unless aluminium bone disease is suspected.

Less invasive methods are available, including plain radiography, which can be used in Australian clinical practice to aid in the diagnosis of renal osteodystrophy. Plain radiographs can be used to detect skeletal changes as a result of renal bone disease. For example, subperiosteal resorption in the phalanges indicates the presence of osteitis fibrosa (Fournier et al 1998). Radiological changes, however, appear late in the course of renal osteodystrophy, and some patients can have severe histological changes but normal radiographs (Roe & Cassidy 2000). Furthermore, radiographs cannot distinguish between high- and low-turnover disease.

Other techniques to aid in the diagnosis of renal osteodystrophy include parathyroid imaging, scintigraphy, bone densitometry (DEXA) and quantitative ultrasound. These latter two techniques, however, measure bone mineral density (BMD) and thus give no information on bone turnover or the variant of bone disease.

Recently, clinicians have used multiple biochemical makers to diagnose renal osteodystrophy. The RIA of intact PTH (iPTH) is the most important. It is increasingly used as a predictor of the type of bone histology (Ferreira 2000). However, serum iPTH levels alone do not provide sufficient information to determine the variant of renal osteodystrophy in the individual patient (Hruska & Teitelbaum 1995). The prediction of bone histology from iPTH assays may become more accurate with the addition of whole PTH (1–84). However, evidence for this is still limited.

The other biochemical markers used can be divided into two major categories reflecting bone formation and resorption (see Table 2). As renal osteodystrophy is characterised by changes in bone formation or osteoblastic activity, these markers have the potential to evaluate bone turnover.

Treatment

Treatment is dependent on the variant of renal osteodystrophy (Kaplan et al 1999). The principles of clinical management include:

- control of serum phosphate and calcium concentration to achieve reference values
- prevention of parathyroid gland hyperplasia
- suppression of PTH secretion to reduce further growth of the parathyroid glands if hyperplasia has occurred
- minimisation of exposure to aluminium
- reversal of the skeletal abnormalities.

Table 18 provides a brief overview of the various treatment strategies for renal osteodystrophy.

Table 18 Summary of treatment options available for types of renal osteodystrophy

High phosphate	High PTH	Adynamic bone disease	Other
Dietary reduction	Normalise serum calcium	PTH ×3–5 upper limit of normal	Bisphosphonates
Dialysis	Calcitriol or other vitamin D preparations	Normalise calcium by	
Phosphate binders:		– ↓ oral calcium or calcitriol	
– Calcium	Reduce serum levels of phosphate	– ↓ calcium in the dialysis fluid	
– Magnesium	Calcimimetics	Avoid aluminium exposure	
– Aluminium	Surgery		
– Sevelamer			

Abbrevation: PTH, parathyroid hormone.
Source: Adapted from information provided by the Renal Resource Centre (2002).

Potential value of Ostase

This review examines the potential role of Ostase in the differential diagnosis of renal osteodystrophy and in the monitoring of treatment in patients with prolonged low renal function. These roles are illustrated in the clinical flow chart in Appendix F.

Little information is available on the role of Ostase in the initial diagnosis of renal bone disease. The greatest potential value for Ostase would be in the differential diagnosis of renal osteodystrophy. Correctly diagnosing the type of renal osteodystrophy is important, as different measures have to be taken. As already mentioned, bone biopsy remains the gold standard for determining the type of renal osteodystrophy in patients with renal insufficiency. This is primarily due to the need for an accurate diagnosis between hyperparathyroidism (HPT) and adynamic bone disease (Fournier et al 1998). The importance of the distinction is that the treatments for the two disorders are completely different, in fact conflicting, and should the wrong diagnosis be made, serious complications could arise for the patient. In patients who are asymptomatic, the differential diagnosis is also important but less urgent, and the decision as to whether to undertake a bone biopsy will depend on whether aluminium exposure is suspected.

Given the invasive nature of bone biopsy and the fact that a significant proportion of patients with low renal function are asymptomatic, non-invasive methods to aid in the differential diagnosis are being continually trialled. Currently, in terms of non-invasive markers, a definitive diagnosis cannot be made from any one test; rather, results from several tests are needed to determine the type of renal osteodystrophy. Two of the most commonly used markers in differentially diagnosing renal osteodystrophy are iPTH and TALP.

As already mentioned, PTH, while being a useful predictor of bone histology, is unable to clearly distinguish adynamic or normal bone from hyperparathyroid bone disease in the individual patient (Qi et al 1995). Therefore, a measure of bone turnover in addition to PTH is needed to allow a more accurate diagnose renal bone disease to be made non-invasively. Generally, the marker that has been used in addition to PTH has been TALP. This marker, however, lacks sensitivity and specificity since about half of its activity is derived from bone and the other half from liver. Therefore, should Ostase be a more specific test than TALP, then a combination of BALP with iPTH may result in increased diagnostic certainty of the different forms of renal bone disease. As a result there may be a decrease in the use of other more expensive or invasive tests in the differential diagnosis of renal osteodystrophy.

In terms of biochemical markers, serum iPTH would seem to be the most widely used marker in monitoring the need for and impact of treatment, specifically calcitriol therapy in renal osteodystrophy (Diaz-Corte & Cannata-Ia 2000). Calcitriol can have a direct effect on bone turnover, so plasma BALP, as measured by Ostase, may have the potential to assist in the decision as to whether calcitriol treatment should be changed.

The measurement of BALP by immunoassay may also be useful in the monitoring of bone formation in renal transplant recipients. Again, PTH has generally been used as a indicator. However, there is some suggestion that BALP may be a more accurate marker of bone metabolism in this group, having the potential to assist in managing patients with impaired renal function (Schmidt-Gayk et al 2001).

Review of the literature

Search strategy

The search strategies used to identify relevant studies for renal osteodystrophy are outlined in the Approach to Assessment section (page 7).

Eligibility criteria

The eligibility criteria used to evaluate abstracts and full papers are shown in Table 19. These criteria relate to the study question as summarised in Appendix E.

Table 19 Eligibility criteria used for renal osteodystrophy articles

Patients	Patients had prolonged low renal function (GFR < 30 mL/min).
Intervention	Papers had to measure BALP by Tandem-R-Ostase, Tandem MP Ostase or Access Ostase. Papers in which BALP was measured by Alkphase B or by electrophoresis were excluded.
Comparator	Biochemical marker, iPTH, TALP
Other	Papers were excluded if fewer than 10 patients were reported on.
	The exception to this may be in the situation where there are no publications with more than 10 patients. Rather than excluding all papers for a clinical indication on the basis of this criterion, available information is reported, noting limitations.
	Review-only / editorial / technical papers were excluded.
	Data available in abstract form only were excluded.
	All non-English papers were excluded.
	Papers which report no clinical results were excluded.

Results

The search of databases and Web sites of international health technology assessment agencies did not identify any relevant health technology assessments for this indication.

This search identified 946 non-duplicate citations relating to renal osteodystrophy.

Seven hundred and eighty-six studies (838 citations) were excluded on the basis of these eligibility criteria.

One hundred and eighty-four studies were excluded on the basis of patient group, 426 studies on the intervention, 11 on the comparator and 165 on other criteria.

Fifty-one additional citations were not excluded in this process, but were used as background papers for various aspects of the review.

Twenty-nine studies that met the eligibility criteria above were then examined in more detail. A further 21 of these studies (22 citations) were excluded because they did not measure BALP using Ostase or did not report on diagnostic accuracy.

Six studies thus form the basis of this review and are summarised in Table 47 in Appendix C. Table 20 outlines the number of papers that address each respective research question for renal osteodystrophy.

Table 20 Renal osteodystrophy publications

Clinical question, name of paper	NHMRC Level	Number
Diagnosis		5
Urena et al (1996)	Level IV	
Fletcher et al (1997)	Level IV	
Coen et al (1998)	Level IV	
Couttenye et al (1996)	Level IV	
Woitge et al (1996)	Level IV	
Treatment monitoring		0
Correlation between histomorphometric parameters and plasma biochemical markers		1
Jarava et al (1996)	Level IV	
Total		**6**

Methodological issues in the studies

As outlined in Appendix G, several factors may compromise a study's validity, and therefore limit the extent to which results can be generalised to clinical scenarios.

The six studies that form the basis of this review were of generally poor methodological quality. The following specific methodological issues limited the extent to which data could be evaluated for the renal osteodystrophy studies included in this review:

- Substantial variation existed within the studies as to the cut-off points used for the markers of TALP, BALP and iPTH.
- Methods of measuring bone isoenzymes varied between papers.
- Although most patients in the papers had a bone biopsy, not all had a biopsy after tetracycline double-labelling, which is necessary to measure rates of bone metabolism.
- Most of the papers had a high percentage of patients with HPT and relatively few patients with adynamic bone disease. This may be because patients with HPT tend to be on dialysis longer than other histological groups. The difficulty is in generalising the results of these studies to broader patient groups.
- Patients with liver complications were usually excluded from test results, which may underestimate the superiority of BALP in comparison to TALP.

- Five of the six papers did not interpret bone biopsy readings independent of biochemistry results.

- None of the papers gave sufficient information for a reader to determine whether patient selection bias was controlled.

Diagnostic accuracy of Ostase

Six papers form the basis of this section. Relevant data regarding the diagnostic accuracy of BALP as measured by Tandem-R-Ostase in determining the diagnosis of renal bone disease is based primarily on three papers (Coen et al 1998; Fletcher et al 1997; Urena et al 1996). These three studies compared serum bone isoenzymes with bone histology and reported the sensitivity and specificity of the former in the diagnosis of renal osteodystrophy. One paper that reported on the incremental value of BALP as measured by electrophoresis is also included (Couttenye et al 1996). Two other papers, one comparing BALP with TALP (Woitge 1996) and one reporting on correlation information (Jarava et al 1996), are also summarised below. Only limited information can be drawn from these latter two papers, as the data reported are outside the scope of the research questions. There were no papers that specifically reported on the role of BALP in the treatment of patients with prolonged low renal function.

Diagnosis

Urena et al (1996) (n = 42) determined the diagnostic value of BALP, measured by Tandem-R-Ostase, in the evaluation of bone turnover in haemodialysis patients. The study includes 42 patients, all of whom had biopsies. Double tetracycline labelling was performed in 17 patients, and each bone section was measured independently of the biochemical marker results. The study population consisted of 30 patients with HTBD and 10 patients with normal or LTBD. Only one patient had adynamic bone disease. The authors report that BALP > 20 ng/mL was a better predictor of HTBD (sensitivity of 100 per cent, specificity of 100 per cent and positive predictive value of 84 per cent) than TALP levels of >200 IU/L (sensitivity of 50 per cent, specificity of 90 per cent and positive predictive value of 94 per cent) or iPTH levels of >200 pg/mL (sensitivity of 72 per cent, specificity of 80 per cent and positive predictive value of 92 per cent). Values of BALP above 20 ng/mL combined with iPTH above 200 pg/mL provided a 94 per cent predictability of HTBD in patients on haemodialysis, with a sensitivity and specificity of 100 per cent and 80 per cent. Given these results, the authors concluded that BALP levels alone or in combination with iPTH may be the best plasma makers of secondary HPT in dialysis patients. However, normal BALP levels were seen in patients with mild HTBD as well as in the one patient with adynamic bone disease. This indicates that BALP may only be of value in select groups of patients, and certainly no definitive conclusions can be drawn regarding the diagnosis of adynamic bone disease with BALP.

Fletcher et al (1997) reported the diagnostic accuracy of BALP, as measured by Ostase, in relation to the diagnosis of HPT. Seventy-three patients from dialysis units were included in the study. All patients had a bone biopsy and 20 also received tetracycline double-labelling, but only 57 biopsies could be histomorphometrically evaluated owing to damage to 16 specimens in the collection process. In terms of the spectrum of renal osteodystrophy present in the study population, 57 patients were identified as having mild, moderate or severe HPT, four had mixed osteodystrophy, three had adynamic bone disease, one had osteomalacia, and the remaining eight patients had normal bone

histology. The authors found that in the diagnosis of HPT, BALP > 10 ng/mL had a sensitivity of 70 per cent and a specificity of 92 per cent. iPTH with a cut-off point of 100 pg/mL had a sensitivity and specificity of 81 and 66 per cent, respectively. When BALP was used in combination with iPTH (> 100 pg/mL), sensitivity decreased to 66 per cent, while specificity increased to 100 per cent. In comparison, TALP > 300 IU/L had a sensitivity of 30 per cent and specificity of 100 per cent; and when it was used in combination with iPTH (> 100 pg/mL), sensitivity and specificity remained the same. The authors noted that in patients with normal histology, low bone turnover and mild HPT, there was no significant difference in BALP, TALP or iPTH levels. Thus, markers of bone turnover were unable to differentiate the bone pathologies in these patients. It would seem from the data provided that patients with normal histology or mild HPT were difficult to differentiate.

Coen et al (1998) investigated the usefulness of a range of biochemical markers in comparison with histomorphometric and histodynamic investigation of bone biopsies in haemodialysis patients (n = 41). Classification of bone histology led to the identification of nine cases of LTBD, nine of mixed osteodystrophy (MO), and 23 of prevalent HPT. Diagnostic sensitivity, specificity and accuracy were reported for various markers using the cut-off point that gave the best results. The sensitivities and specificities for iPTH using a cut-off point of 79.7 pg/mL reported in the body of the paper were different from the values reported in the abstract. It is assumed that the correct values were those reported in the body of the paper, where sensitivity and specificity were reported as 88.8 and 93.7 per cent respectively, with an accuracy of 92.7 per cent in the discrimination of LTBD and mixed osteodystrophy/HPT. According to the investigators, BALP gave the highest accuracy of 95.1 per cent with a sensitivity of 100 per cent and a specificity of 93.8 per cent at a cut-off of 13 ng/mL. In comparison TALP, with a threshold of 82.5 U/L, had an accuracy of 94.8 per cent, a sensitivity of 75 per cent and a specificity of 100 per cent in the differentiation of LTBD and mixed osteodystrophy/HPT. When iPTH and BALP were used in combination, a correct classification of mixed osteodystrophy/ HTBD and LTBD was possible in 90.6 per cent and 88.9 per cent of patients respectively. With the combination of iPTH and TALP, correct classification of mixed osteodystrophy/HTBD was possible in 81.3 and 88.9 per cent of patients, respectively. The authors noted that TALP would seem to be slightly less valid than BALP. However, the study excluded patients with cholestatsis, and so the predictive value of BALP may be underestimated.

Although Couttenye et al (1996) did not use Ostase to measure BALP, the study does provide some useful information on the clinical utility of BALP in the diagnosis of adynamic bone disease. The authors reported on the results of 103 chronic haemodialysis patients. All patients had a bone biopsy with double tetracycline labelling. The bone isoenzyme was determined by an agarose gel electrophoretic method; iPTH, TALP and osteocalcin (OC) were also measured. The index point of sensitivity was chosen at a level where the highest sensitivity with the highest specificity was found. The histological results revealed that the population included 21 patients with HPT, 38 with adynamic bone disease, 10 with osteomalacia, 21 with mixed disease and 13 with normal histology. For the diagnosis of adynamic bone disease, BALP ≤ 27 ng/mL was found to have a sensitivity of 78.1 per cent and a specificity of 86.4 per cent, compared with iPTH (150 pg/mL) with a sensitivity and specificity of 80.6 and 76.2 per cent. When BALP was used in combination with iPTH ≤ 150 pg/mL, sensitivity was decreased (67.7%), while specificity increased to 91.5 per cent. The authors also noted that although BALP and iPTH displayed similar sensitivities, a low BALP test had less false positives, which disappeared when the two tests were combined. The authors reported that the false

positives obtained by BALP came from five normal patients, two patients with osteomalacia and one with a mixed lesion. In contrast, 71.4 per cent of the false negative patients (n = 5) had evidence of aluminium overload despite having BALP > 27 ng/mL. The authors noted, however, that the results of this study indicated that a finding of a low BALP excludes with a high degree of certainty the diagnosis of HPT. One problem with this study is that not all patients' results (n = 103) were reported for each marker. Whereas 91 patients had a test result for BALP and 99 had an iPTH test result, only 90 had both iPTH and BALP results.

Table 21 outlines the results of the studies included in this section.

Table 21 Sensitivity and specificity of the different biochemical markers used in the diagnosis of renal osteodystrophy

	iPTH				TALP				BALP				iPTH + TALP				iPTH + BALP			
	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV
Urena et al (1996)[a]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
HTBD	72%	80%	92%	47%	50%	90%	94%	36%	100%	100%	84%	100%	NR	NR	NR	NR	100%	80%	94%	100%
LTBD	80%	72%	47%	92%	90%	50%	36%	94%	100%	100%	100%	84%	NR	NR	NR	NR	80%	100%	100%	94%
Coen et al (1998)[b]	88.8%	93.7%	–	–	75%	100%	–	–	100%	93.8%	–	–	81%	89%	96%	57%	91%	89%	96.7%	73%
MO / HTBD																				
Fletcher et al (1997)[c]	81%	66%	–	–	30%	100%	–	–	70%	92%	–	–	30%	100%	–	–	66%	100%	–	–
HPT bone disease																				
Couttenye et al (1996)[d]	80.6%	76.2%	65%	88%	75%	83%	–	–	78.1%	86.4%	75%	88%	–	–	–	–	68%	92%	–	–

Abbreviations: HTBD, high-turnover bone disease; HPT, hyperparathyroidism; LTBD, low-turnover bone disease; MO, mixed osteodystrophy; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

[a] Using a cut-off of iPTH 200 pg/nL, TALP 200 IU/L, BALP 20 ng/mL; [b] using a cut-off of iPTH 79.7 pg/nL, TALP 82.5 IU/L, BALP 13 ng/mL; [c] using a cut-off of iPTH 100 pg/nL, TALP 300 IU/L, BALP 10 ng/mL; [d] using a cut-off of iPTH 150 pg/nL, TALP 123 IU/L, BALP 27 ng/mL.

Woitge et al (1996) also provided some limited information on the role of BALP in patients with impaired renal function. The study compared TALP with three different assays of serum BALP in both healthy adults (n = 119) and patients with non-skeletal disorders or metabolic bone diseases (n = 236). Patients with chronic renal failure (n = 47) and secondary HPT (n = 35) were included in the study. However, the results are reported separately. In patients with secondary HPT, ROC curve analysis indicated that the areas under the curve for TALP and BALP were 0.689 and 0.601, respectively. Caution, however, should be exercised in applying these results to all patients with renal osteodystrophy. The paper also did not provide any information on the incremental benefit of BALP to other biochemical makers.

Correlation between histomorphometric parameters and plasma biochemical markers

Jarava et al (1996) provided some useful information, but not in relation to diagnostic accuracy. Four biochemical markers (iPTH, AP, OC and BALP, as measured by Tandem-R-Ostase) were measured in patients with chronic renal insufficiency being treated with haemodialysis (n = 56). Twenty of these patients received a bone biopsy, which revealed severe osteitis fibrosa in 15 cases, mild osteitis fibrosa in two cases, one case of adynamic bone disease, one mixed lesion and one normal finding. The highest correlation of bone histology, both formation and resorption was with iPTH and BALP. Note, however, that most patients in the study had osteitis fibrosa, and none of the patients, according to the authors, had any clinical evidence of liver disease. This limits the generalisability of these results to a wider spectrum of patients with renal osteodystrophy.

Treatment monitoring

Little is reported in relation to the role of BALP, as measured by Ostase, in the monitoring of treatment in patients with impaired renal function. Withold, Friedrich, and Degenhardt (1997) suggested that BALP, compared with OC and osteonectin, might provide more useful information about bone formation in patients receiving renal transplantation, as BALP values correlated significantly with osteotropic hormone levels, and mean BALP values varied significantly during a three-month follow-up after surgery. Other papers also reported on the level of BALP after various treatments (Gonzalez et al 1995)(Reinhardt et al 1998; Ritz et al 1995). However, none of these reports provided information about diagnostic accuracy for BALP in monitoring treatment. Further research is required in this area to define the role in BALP in the monitoring of treatment in patients with prolonged renal insufficiency.

Impact of Ostase on clinical management

No specific information was contained in the papers regarding therapeutic impact of Ostase on clinical management of renal osteodystrophy. It is possible, however, that Ostase may play a role in determining optimal treatment options by more accurately diagnosing the variant of renal osteodystrophy or by providing additional information about the bone turnover rates during treatment. However, this is yet to be reported on in the literature.

Impact of Ostase on patient outcomes

No studies reported on the impact of BALP, as measured by Ostase, on patient outcomes. It may be that Ostase could result in improved health outcomes, but as the evidence is currently limited it is difficult to draw conclusions about the role of Ostase. It should be remembered that improved diagnostic accuracy does not necessarily translate into improved health outcomes. Good quality studies are needed to ascertain the role of such measures in the improvement of health outcomes in patients with impaired renal function.

Conclusions

- The conclusions regarding the diagnostic accuracy of BALP in the differential diagnosis of renal osteodystrophy are based on a relatively small body of evidence.
- A number of methodological limitations exist in the studies reporting on BALP and renal osteodystrophy.
- On the basis of the evidence presented it would appear that Ostase could play a role in the differential diagnosis of renal osteodystrophy. In the populations reported on it would seem that the diagnostic accuracy of BALP alone or in combination with iPTH is better than that of TALP alone or TALP and iPTH combined. However, it is difficult to generalise the results given the small number of patients with adynamic bone disease reported on in the studies.
- Further evidence is needed in terms of the role of Ostase in the monitoring of treatment response.
- There is insufficient evidence at this time to indicate the role of Ostase in improving health outcomes and altering management of patients with impaired renal function.

Prostate cancer

The clinical problem

The following review assesses the role and value of Ostase in relation to prostate cancer. Specifically, the following clinical questions are addressed:

- What is the additional value of Ostase to PSA and TALP in determining the extent of bone metastases as detected on bone scans (i) in the initial staging of disease, and (ii) during follow-up after treatment in patients with prostate cancer?

- What is the additional value of Ostase to PSA and TALP in the monitoring of therapy in patients with prostate cancer and bone metastases?

Bone is the most common site of metastasis from prostate cancer. The determination of bone metastases is important in the initial staging of prostate cancer, as this could have implications for treatment management. During follow-up, the early detection and treatment of metastatic disease may also reduce the morbidity associated with bone metastases and could potentially prolong survival.

For initial staging, a variety of tests are currently available to assist in the detection and diagnosis of bone metastases. Radionucleotide bone scans can detect changes in bone metabolism that may indicate metastatic bone disease. However, X-rays, computer tomography, magnetic resonance imaging and biopsy are required in order to confirm the diagnosis. Furthermore, although bone scans are commonly used to assist during initial staging, it is not feasible to institute repetitive scans to screen for metastases during follow-up. This is because bone scans, lacking the specificity to delineate between bone metastasis and other metabolic bone disorders, are less likely to be cost-effective. There are also problems associated with increased radiation exposure, as bone scans require the administration of a radioisotope dye.

Patients diagnosed with bone metastases may require symptomatic treatment. Response to therapy is largely determined by evaluating the degree of symptomatic relief. X-rays and radionucleotide bone scans can also be used, but as these techniques lack sufficient sensitivity and specificity to detect changes in metabolic activity, quantitative assessment is limited.

Biochemical markers of bone metabolism such as TALP and BALP may have the potential to provide additional information on bone turnover and therefore assist in the detection and monitoring of bone metastases in prostate cancer.

Epidemiology and clinical presentation

In Australia, prostate cancer is the most common malignant cancer of males, commonly affecting older men. In 1999, there were 10,232 new registrable cases of prostate cancer reported, representing an age-standardised incidence rate of 110 per 100,000 population (Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR) 2002). Since the early 1990s the incidence of prostate cancer has increased in Australia. This is possibly attributable to increased early detection rates

with the use of PSA screening. However, the increase in incidence has peaked in recent years (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2000; Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR) 2002). In 1999, there were approximately 2,500 deaths from prostate cancer, thus representing an age-standardised mortality rate of 28 per 100,000 population and 54,700 man-years of life lost (Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR) 2002). Five-year survival rates have improved for prostate cancer; this may be due to earlier disease detection and improved treatment (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2000).

Considerable uncertainty exists as to the risk factors associated with prostate cancer. It is therefore difficult to identify specific groups of men that may be more likely to develop the disease. Potential factors that have been identified include geographic and racial differences, high fat diet, and genetic and familial factors. Selenium supplementation and the dietary impact of phyto-oestrogens may have a protective role against prostate cancer, but this has yet to be supported in large randomised clinical trials (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2000).

Detection of locally confined, non-metastatic prostate cancer is usually not based on patient symptoms, but rather through 'screening' investigations or incidentally via other unrelated examinations and surgical interventions. Such tumours are usually asymptomatic as they are slow growing and do not cause early obstruction. Symptoms may occur, however, and include slow stream, hesitancy, frequency and urgency of micturition, perineal discomfort, and acute or chronic urinary retention (Horwich, Jonathan, & Schroder 1995).

Between 65 and 75 per cent of prostate cancers will metastasise to bone (Coleman 2001). These lesions can lead to significant pain and morbidity, and men diagnosed with metastatic disease generally cannot be cured. Complications associated with bone metastases include pathological fractures, hypercalcaemia, impaired mobility, spinal cord or nerve root compression, and bone marrow infiltration (Coleman 2001; Hamdy 2001). Decreased performance status, tumour-related anorexia and anaemia may present as initial symptoms and usually indicate advanced disease (Horwich, Jonathan, & Schroder 1995).

Survival of men with prostate cancer is related to tumour extent at diagnosis. Men diagnosed with locally confined, well-differentiated prostate cancer have a better prognosis than men diagnosed as having metastatic prostate cancer. Given the natural history of prostate cancer, older men with well-differentiated disease are more likely to die from other causes unrelated to their prostate cancer. Other factors that have been identified as important in predicting prognosis include patient's age, comorbidities, Gleason grade, level of serum acid phosphatase, level of PSA, extent of tumour spread, and lymph node and other metastases (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2000; Coleman 2001).

Conventional diagnosis and treatment

Diagnosis and staging

Prostate cancer is diagnosed via prostatic biopsy. Clinical staging will assist in initial treatment decisions and is generally determined by using a variety of clinical and pathological tests, including histologic analysis, PSA levels, digital rectal examination, and imaging techniques such as computer tomography and magnetic resonance imaging. Radionucleotide bone scans are widely used to test for the presence of bone metastases. The vast majority of tumours diagnosed are adenocarcinomas (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2000).

The revised TNM (tumour, node, metastasis) system used by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer in 1997 is commonly used to stage prostate cancer (American Joint Committee on Cancer 1997). However, owing to a lack of good quality evidence on the natural history of the disease and the difficulty in differentiating between tumour types, many men are not correctly staged. The literature suggests that understaging occurs in 40 to 65 per cent of men diagnosed as having clinically localised disease, in 63 per cent of men with extracapsular extension, in 23 per cent of men with cancer-positive surgical margins and in 8 per cent of men who have positive lymph nodes (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2000). The AJCC system is outlined in Table 22.

Table 22 American Joint Committee on Cancer (AJCC) staging for prostate cancer

Stage	Characteristics
Stage I	T1a, N0, M0, G1
Stage II	T1a, N0, M0, G2, 3–4
	T1b, N0, M0, Any G
	T1c, N0, M0, Any G
	T1, N0, M0, Any G
	T2, N0, M0, Any G
Stage III	T3, N0, M0, Any G
Stage IV	T4, N0, M0, Any G
	Any T, N1, M0, Any G
	Any T, Any N, M1, Any G
Primary tumour (T)	
TX: Primary tumour cannot be assessed	
T0: No evidence of primary tumour	
T1: Clinically unapparent tumour not palpable or visible by imaging	
T1a: Tumour incidental histologic finding in 5% or less of tissue resected	
T1b: Tumour incidental histologic finding in more that 5% of tissue resected	
T1c: Tumour identified by needle biopsy (eg, because of elevated PSA)	
T2: Tumour confined within prostate[a]	
T2a: Tumour involves one lobe	
T2b: Tumour involves both lobes	
T3: Tumour extends through the prostatic capsule[b]	
T3a: Extracapsular extension (unilateral or bilateral)	
T3b: Tumour invades the seminal vesicle(s)	
T4: Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	
Regional lymph nodes (N)	
NX: Regional lymph nodes (ie, lymph nodes of the true pelvis) cannot be assessed	
N0: No regional lymph node metastasis	
N1: Metastasis in regional lymph node or nodes	
Distant metastasis (M)	
MX: Distant metastasis cannot be assessed	
M0: No distant metastasis	
M1: Distant metastasis	
M1a: Non-regional lymph nodes	
M1b: Bone(s)	
M1c: Other site(s)	
Note: When more than one site of metastasis is present, the most advanced category is present (pM1c) is used.	
Histopathologic grade (G)	
GX: Grade cannot be assessed	
G1: Well differentiated (slight anaplasia)	
G2: Moderately differentiated (moderate anaplasia)	
G3–4: Poorly differentiated or undifferentiated (marked anaplasia)	

[a] Tumour found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified T1c.
[b] Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.
Source: Australian Cancer Network Working Party on Management of Localised Prostate Cancer (2000).

Treatment

Clinically localised disease

Treatment options for men diagnosed with locally confined prostate cancer can be divided into three broad categories: (i) radical prostatectomy, (ii) radical radiotherapy (including brachytherapy or conformal radiotherapy) and (iii) no initial treatment. Adjuvant hormone therapy may also be prescribed with surgery or radiotherapy. Adverse events associated with surgery or radiotherapy include urinary incontinence, impotence, urethral stricture, and less commonly rectal complications, including faecal incontinence, rectal bleeding and tenesmus (desire to defaecate). Table 23 outlines the treatment options for different patient groups with clinically localised prostate cancer. Currently, as there is no information from randomised controlled trials (only data from case-series and cohort studies), it is not possible to clearly ascertain the relative effectiveness of these treatment approaches in terms of survival. Therefore, physicians and patients need to weigh up the potential benefits and risks of treatment for each individual.

Table 23 Treatment options for different patient groups with clinically localised prostate cancer

Patient group	Treatment options
Younger men (> 10 years life expectancy)	Radical prostatectomy, radical radiotherapy or brachytherapy
Medically fit	Clinical observation
Older men (< 10 years life expectancy), or	No initial therapy
Men presenting with well to moderately differentiated tumours	Treatment may be prescribed as symptoms arise

Source: Australian Cancer Network Working Party on Management of Localised Prostate Cancer (2000).
Note: As there is currently poorer-quality evidence comparing treatment options, it is not possible to clearly determine the relative effectiveness of these treatment approaches in terms of survival. Decisions about treatment may also be based on patient preference and individual risk–benefit ratios.

Advanced prostate cancer

Men are diagnosed as having advanced disease when there is metastatic spread of the tumour beyond the prostate capsule. As previously outlined, bone is a common site for prostate metastasis. Men with advanced disease do not usually undergo radical prostatectomy, but are treated with hormone therapy (chemical or surgical androgen ablation). As men are rarely cured of advanced prostate cancer, the primary treatment objectives are directed towards symptom relief and prolonging survival.

A systematic review of four randomised clinical trials (n = 2167) found that men with advanced prostate cancer treated with immediate hormonal treatment had improved overall survival and were less likely to have complications as a result of the cancer than men receiving deferred hormonal treatment. A statistically significant difference was not found between the two groups for survival from prostate cancer, but a potential clinical difference could not be excluded. The results of this review suggest that men with advanced prostate cancer may benefit from immediate hormonal treatment, but the authors suggest that further research is required to evaluate the risks and benefits of prolonged hormone therapy in terms of adverse events and costs (Nair 2002).

As symptoms arise, men with metastatic disease may receive other treatments. Urethral or bladder obstruction can be treated with radiotherapy and palliative surgery (transurethral resection). Pain arising from bone metastases may benefit from external beam radiation and/or bone-seeking radionucleotides such as strontium-89 (Porter et al 1993; Robinson 1993). Bisphosphates may also have a role in reducing pain associated

with bone metastases as they assist in slowing abnormal bone turnover and hence tumour growth (Coleman 1998).

Hormone refractory disease develops when patients do not respond to hormone therapy. At present, the use of chemotherapy for hormone refractory disease is still under evaluation. So far there is insufficient evidence to support the use of chemotherapy outside clinical trials, because although it appears to improve response rates, it does not appear to prolong survival (Hudes et al 1992; Millikan 1999; Pienta et al 1994). Other drugs, including non-steroidal anti-inflammatory drugs, opiates and bisphosphonates, may be given to manage pain and osteoporosis (National Cancer Institute 2002).

Local or regional recurrence management will depend on prior treatment, site of recurrence, comorbidities and individual patient preferences. Treatment may include hormonal treatment, surgery, radiotherapy or a combination of therapies deemed appropriate. Other drugs that offer palliative relief may also be prescribed (National Cancer Institute 2002).

Adverse events that have been associated with hormonal treatment include exacerbation of cardiovascular disease, thrombo-embolitic complications, psychological implications of orchiectomy (surgical castration), hot flushes, gynecomastia, osteoporosis, and nausea and vomiting (National Cancer Institute 2002).

Treatment monitoring for men with bone metastases

The primary aim of treatment for metastatic disease in prostate cancer is to provide relief from symptoms. Therefore, symptom relief is the most important clinical outcome used to monitor the effectiveness of metastatic treatment. Other secondary outcome measures determined radiologically may also be used. The World Health Organization (WHO) has proposed response criteria for the evaluation of cancer treatment for bone metastases (Table 24). These criteria are based on X-ray or bone scan results. WHO claims that X-ray and bone scan results are equivalent, but some studies suggest that bone scans may be less reliable, especially when used within the first months following treatment. Although bone scans may be more sensitive in detecting bone changes than plain film, bone scans may be less able to differentiate between increased metabolic activity and bone healing. Therefore, changes detected on bone scans should be verified by plain film, computed tomography or magnetic resonance imaging before clinical decision-making (Blomqvist 2001; Coleman 1998).

Table 24 World Health Organization (WHO) response criteria for bone metastases

Complete response	Complete disappearance of all lesions on X-ray or scan for at least 4 weeks.
Partial response (decrease in metastatic size of <50%)	Partial decrease in size of lytic lesions, recalcification of lytic lesions or decreased density of blastic lesions for at least 4 weeks.
No change	No significant change for at least 4 weeks. Because of the slow response of bone lesions, the designation 'no change' should not be applied until at least 8 weeks have passed from the start of therapy.
Progressive disease	Increase in size of existent lesions or appearance of new lesions.
Occurrence of bone compression or fracture should not be used as the sole indicator for evaluation of therapy.	

Source: Blomqvist (2001).

Potential value of Ostase

This review examines the potential role of Ostase in (i) diagnosing bone metastases at initial staging and during follow-up of prostate cancer, and (ii) determining treatment response in patients with prostate cancer bone metastases. These roles are illustrated in the clinical flow chart in Appendix F.

Prostate cancer bone metastases are predominantly characterised by increased bone formation or osteoblastic activity. Some studies have found that BALP levels are significantly elevated in men with bone metastases from prostate cancer compared with men without bone metastases (Lorente et al 1996; Lorente et al 1999; Morote, Lorente, & Encabo 1996; Wechsel, Petri, & Bichler 1997). As Ostase measures the levels of serum BALP, a bone formation marker, this test may be able to detect early metabolic changes indicative of prostate bone metastases.

Patients diagnosed with bone metastases may require symptomatic treatment. Response to therapy is largely determined by evaluating the degree of symptomatic relief. X-rays and radionucleotide bone scans can also be used, but as these techniques lack sufficient sensitivity and specificity to detect changes in metabolic activity, quantitative assessment is limited. BALP as measured by Ostase may provide an alternative for monitoring treatment prescribed to men with prostate cancer bone metastases.

However, at this stage, it is unclear whether Ostase would provide any useful additional information, as there is insufficient evidence to suggest that the institution of early treatment in asymptomatic patients with prostate cancer diagnosed with bone metastases confers any overall benefit. Further research is still required to more definitively evaluate the efficacy and adverse effects of early versus late therapy.

Review of the literature

Search strategy

The search strategies used to identify relevant studies for prostate cancer are outlined in the Approach to Assessment section (page 7).

Eligibility criteria

The eligibility criteria used to evaluate abstracts and full papers are shown in Table 25. These criteria relate to the study question as summarised in Appendix E.

Table 25 Eligibility criteria for prostate cancer

Patients	Patients had prostate cancer, including: newly diagnosed, untreated treated patients undergoing follow-up.
Intervention	Papers had to measure BALP by Tandem-R-Ostase, Tandem MP Ostase or Access Ostase. Papers in which BALP was measured by Alkphase B or by electrophoresis were excluded.
Comparator	Biochemical markers: prostate-specific antigen (PSA) and serum total alkaline phosphatase (TALP)
Other	The outcome measure had to be relevant to the study question. Papers were excluded if fewer than 10 patients were reported on. The exception to this may be in the situation where there are no publications with more than 10 patients. Rather than excluding all papers for a clinical indication on the basis of this criterion, available information is reported, noting limitations. Review-only / editorial / technical papers were excluded. Data available in abstract form only were excluded. All non-English papers were excluded. Papers which report no clinical results were excluded.

Results

The search identified 344 non-duplicate citations relating to prostate cancer.

Two hundred and fifty-two studies (273 citations) were excluded on the basis of these eligibility criteria.

Fourteen studies were excluded on the basis of patient group, 124 studies on intervention, 114 studies on other criteria.

An additional 16 papers were not excluded in this process, but were used as background papers for various aspects of the review.

Fifty studies (55 citations) were then examined in more detail, as it was not possible to determine their eligibility from abstracts. A further 50 studies (51 citations) were excluded as they did not measure BALP using Ostase or did not report diagnostic accuracy.

The four studies that form the basis of this review are summarised in Table 48 and Table 49 in Appendix C. These papers report on the combined diagnostic value of BALP with PSA, providing information that is more useful than papers that report on the replacement value of BALP. It is likely that BALP will be used in addition to markers (eg, PSA and TALP) and other clinical information when decisions about the diagnosis of bone metastases in patients with prostate cancer are formed.

An additional six papers were also identified (Akimoto et al 1998; Diaz-Martin et al 1999; Jung et al 2001; Wolff et al 1996; Wolff et al 1998; Wolff et al 1999), but after reviewing these papers, it was ascertained that they did not directly address the clinical question. These papers investigated the replacement value rather than the incremental value of BALP in men with prostate cancer. Consequently, they were not included in this review.

No papers were identified that investigated the role of Ostase in treatment monitoring.

Table 26 outlines the number of papers that address each respective research question for prostate cancer.

Table 26 Prostate cancer publications

Clinical question, name of paper	NHMRC level	Number
Diagnosis:		4
Additional value of Ostase		
Morote et al (1996)	Level IV	
Lorente et al (1999)	Level IV	
Lorente et al (1996)	Level IV	
Murphy et al (1997)	Level IV	
Treatment monitoring		0
Total		**4**

Methodological issues in the studies

As outlined in Appendix G, several factors may compromise a study's validity, and therefore limit the extent to which the results can be generalised to clinical scenarios.

The four case series that form the basis of this review were of generally poor methodological quality. The following methodological issues limited the extent to which data could be evaluated:

- It is unclear from all papers as to whether the test and reference standards were measured independently.
- It is unclear from all papers as to whether the test(s) were measured independently from all other clinical information.
- It is unclear from the papers whether Ostase was measured independently of other test results.
- An imperfect reference standard was used in all papers. Although diagnosis of bone metastases by radionucleotide scans represents a practical alternative to bone biopsy, scan results are likely to show some inaccuracy, which is likely to affect the diagnostic accuracy of the test under investigation.
- There was some variation between the studies as to the cut-off points used for BALP, PSA and TALP.
- Sample groups did not represent consecutive series. It is difficult to determine the extent to which patient selection affected the study results (Lorente et al 1996; Morote, Lorente, & Encabo 1996; Murphy et al 1997).
- Sample groups often represented a select group of patients. Patients for whom a definitive diagnosis could not be determined (Lorente et al 1999; Morote, Lorente, & Encabo 1996) or patients who presented with other metabolic bone comorbidities (Lorente et al 1996) were excluded from the studies. This limits the extent to which results can be generalised to clinical populations.

Diagnostic accuracy of Ostase

Disease staging

For initial staging before treatment

Morote et al (1996) (n = 140) investigated the usefulness of BALP and PSA to detect bone metastases in patients newly diagnosed with prostate cancer. Diagnostic accuracy was determined for each marker independently and in combination for a range of cut-off values and was compared with bone scan findings. The results for the combined effects of PSA and BALP are reported here, as this is directly relevant to the research question for this review. When a negative test was defined as BALP < 20 ng/mL and PSA < 20 ng/mL, the tests were concordant with bone scan findings in 136 (97%) of the 140 patients. This produced a sensitivity of 100 per cent, a specificity of 94 per cent, a positive predictive value of 94 per cent and a negative predictive value of 100 per cent. When a negative test was defined as BALP < 30 ng/mL and PSA < 20 ng/mL, the two tests were concordant with bone scan findings in 138 (99%) of the 140 patients. This produced a sensitivity of 99 per cent, a specificity of 99 per cent, a positive predictive value of 99 per cent and a negative predictive value of 99 per cent.

Lorente et al (1999) (n = 295) investigated the usefulness of BALP in addition to PSA in the detection of bone metastases in a consecutive series of untreated patients newly diagnosed with prostate cancer. It appears that this study is an extension of the study conducted by Morote et al (1996) and therefore possibly includes the same patient group. Diagnostic accuracy was determined for each marker independently and in combination for a range of cut-off values and was compared with bone scan findings. The results for the combined effects of PSA and BALP are reported here, as this is directly relevant to the research question for this review. When a negative test was defined as BALP < 20 ng/mL and PSA < 20 ng/mL, the tests were concordant with bone scan findings in 188 (64%) of the 295 of patients. This produced a sensitivity of 100 per cent, a specificity of 47 per cent, a positive predictive value of 47 per cent and a negative predictive value of 100 per cent.

Table 27 outlines the results from the studies that evaluated the additional value of BALP in the detection of bone metastases in patients newly diagnosed with prostate cancer.

Table 27 Detection of bone metastases in the initial staging of prostate cancer patients

Study	*n*	Cut-off value	BALP					PSA					BALP + PSA				
			Sn	Sp	PPV	NPV	Acc	Sn	Sp	PPV	NPV	Acc	Sn	Sp	PPV	NPV	Acc
Morote et al (1996)	140	BALP (> 20 ng/mL) PSA (> 20 ng/mL)	93	88	88	93	90	97	31	57	92	63	100	94	94	100	97
		BALP (> 30 ng/mL) PSA (> 20 ng/mL)	79	99	98	84	89	97	31	57	92	63	99	99	99	99	99
		PSA (> 10 ng/mL)	–	–	–	–	–	99	10	50	88	53	–	–	–	–	–
Lorente et al (1999)	295	BALP (> 20 ng/mL) PSA (> 20 ng/mL)	86	93	84	94	91	97	48	46	97	64	100	47	47	100	64

Abbreviations: Acc, accuracy; BALP, bone alkaline phosphatase; NPV, negative predictive value; PPV, positive predictive value; PSA, prostate-specific antigen; Sn, sensitivity; Sp, specificity.

Staging during follow-up

Lorente et al (1996) (n = 100) investigated the usefulness of BALP and/or PSA in the detection of bone metastases in untreated and treated patients newly diagnosed with prostate cancer as compared with bone scan findings. When a negative test was defined as BALP < 30 ng/mL and/or PSA < 100 ng/mL, the tests were concordant with bone scans in 98 per cent of the patients, thus resulting in a sensitivity of 96 per cent, a specificity of 100 per cent, a positive predictive value of 100 per cent and a negative predictive value of 96 per cent. The authors also reported on a small follow-up study involving 48 men with prostate cancer. Of the three patients that developed bone metastases, all had BALP levels > 30 ng/mL, and two had PSA levels > 100 ng/mL.

Murphy et al (1997) (n = 70) investigated the usefulness of a range of bone markers in the detection of bone metastases in untreated and treated patients newly diagnosed with prostate cancer as compared with bone scan findings. The paper provided only limited useful information for this review. The authors reported on the diagnostic accuracy of BALP in addition to PSA. When a positive test was defined as BALP > 18 ng/mL and PSA > 16 ng/mL, sensitivity was 57 per cent and specificity was 66 per cent compared with bone scan.

Table 28 outlines the results from the studies that evaluated the additional value of BALP in the detection of bone metastases in untreated and treated men with prostate cancer.

Table 28 Detection of bone metastases in patients with prostate cancer (untreated and treated)

Study	*n*	Cut-off value	BALP					PSA					BALP + PSA				
			Sn	Sp	PPV	NPV	Acc	Sn	Sp	PPV	NPV	Acc	Sn	Sp	PPV	NPV	Acc
Lorente et al (1996)	100	BALP (> 30 ng/mL) PSA (> 100 ng/mL)	88	100	100	90	94	79	85	83	82	82	96	100	100	96	98
Murphy et al (1997)	70	BALP (> 18 ng/mL) PSA (> 16 ng/mL)	–	–	–	–	–	–	–	–	–	–	57	66	–	–	–

Abbreviations: Acc, accuracy; BALP, bone alkaline phosphatase; NPV, negative predictive value; PPV, positive predictive value; PSA, prostate-specific antigen; Sn, sensitivity; Sp, specificity.

Treatment monitoring

The search conducted for this review identified no evidence to answer the specific research question of whether the measurement of BALP by Ostase is of any value in monitoring treatment for prostate cancer. However, a number of studies provide some useful information. One study found that BALP levels were significantly associated with pain scores in men with advanced disease (Berruti et al 2000), and another study reported that BALP appears to reduce in response to bisphosphonate therapy (Costa et al 2002). Morote, Bellmunt, and Newling (2002) also found that low BALP as measured by Ostase was a significant independent predictor of an antiandrogen withdrawal effect in a small group of 46 patients in whom maximum androgen blockage failed. Thus, BALP, as measured by Ostase, may work as a marker of disease severity and therefore have the potential to assist in treatment decisions by providing additional information on the treatment response. However, these studies also indicate that the usefulness of BALP may be limited. Berruti et al (2000) found that BALP levels were not able to predict future skeletal complications, and Costa et al (2002) found that BALP was not significantly associated with disease progression in cancer patients. Furthermore, Morote et al (2002) concluded that a prospective study enrolling a larger number of patients would be required to determine a threshold of BALP that would identify patients with a very low probability of responding to anti-androgen withdrawal.

Impact of Ostase on clinical management

At initial staging, detection of bone metastases with Ostase has the potential to alter clinical management by (i) reducing the need to prescribe bone scans for patients classified as having low BALP levels, and (ii) influencing whether patients undergo local or systemic treatment. Men with localised disease may be more likely to have surgery or radiotherapy, whereas men with metastatic disease may be more likely to have systemic hormonal treatment. However, as there is limited evidence evaluating the relative effectiveness of such treatments, it is unclear at this stage whether treatment management decisions determined by Ostase would confer any benefit in patient outcomes.

During follow up after initial staging and treatment, Ostase may have the potential to help prevent the development of complications associated with bone metastases through early detection. If Ostase is able to detect bone metastases earlier, then treatment could be initiated before the onset of substantial bone destruction. However, it is unclear from

current literature whether instituting treatment earlier in asymptomatic patients with metastatic disease confers any overall benefit. While recent evidence suggests that instituting anti-androgen therapy early in patients with advanced prostate cancer reduces disease progression and provides a small improvement in overall survival (Nair 2002), further research is still required to more definitively evaluate the efficacy and adverse effects of early versus late hormone therapy.

Further evidence evaluating how BALP as measured by Ostase facilitates decisions regarding treatment is still required.

Impact of Ostase on patient outcomes

There is insufficient evidence on the role of Ostase in improving health outcomes in patients with prostate cancer. Few studies were identified in the search conducted for this review that reported on the impact of BALP, as measured by Ostase, on patient outcomes. As mentioned above, these studies found that BALP as measured by Ostase was not able to predict future skeletal outcomes (Berruti et al 2000) or disease progression in cancer patients (Costa et al 2002). Long-term prospective studies are required to ascertain any role for Ostase in the improvement of health outcomes in patients with bone metastases of prostate cancer.

Conclusions

- The conclusions regarding the diagnostic accuracy of BALP as measured by Ostase in the diagnosis and treatment monitoring of bone metastases of prostate cancer are based on a very small amount of evidence.

- In the populations reported on in the above studies, BALP as measured by Ostase in combination with PSA appears to have a higher sensitivity and specificity than BALP or PSA alone in the detection of bone metastases at initial staging and during follow up. However, the extent to which conclusions can be drawn from the available evidence is limited by the presence of methodological biases in the studies.

- There is limited evidence at this time to indicate the role of Ostase in the monitoring of treatment responses in patients with bone metastases of prostate cancer.

- There is currently insufficient evidence to indicate the role of Ostase in improving health outcomes and altering management of patients with bone metastases of prostate cancer.

- At this stage there is insufficient evidence to suggest that the institution of early treatment in asymptomatic patients with prostate cancer diagnosed with bone metastases confers any overall benefit. Further research is still required to more definitively evaluate the efficacy and adverse effects of early versus late therapy.

Osteoporosis

The clinical problem

The following review assesses the role and value of Ostase in relation to osteoporosis. Specifically, the following clinical questions are addressed:

- What is the utility of Ostase in assessing fracture risk in patients with low BMD or known to be at risk of osteoporosis?

- What is the utility of Ostase in monitoring therapy in patients with osteoporosis or known to be at risk of osteoporosis?

The specific issue to be addressed is whether the measurement of BALP by Ostase adds any additional useful information to what would be known from the measurement of BMD by dual X-ray absorptiometry (DEXA). In terms of the assessment of fracture risk, the groups of special interest are (i) patients who have a BMD in the osteopenic range (T score between –1 and –2.5 (World Health Organization 1994)), and (ii) peri- or postmenopausal women who have not experienced a previous osteoporotic fracture. In terms of monitoring therapy, the group of interest is patients undergoing pharmacotherapy to prevent or minimise fracture or bone loss.

Epidemiology and clinical presentation

Osteoporosis has been defined as a 'skeletal disorder characterised by compromised bone strength predisposing a person to increased risk of fracture' (NIH Consensus Development Panel on Osteoporosis Prevention 2001). Bone strength is a result of a combination of bone density (as measured by densitometry and expressed as grams of mineral per area of volume) and bone quality, which includes bone microarchitecture, rate of bone turnover, accumulation of microdamage and mineralisation. Fracture results when a force (eg, trauma) is applied to osteoporotic bone. Skeletal sites at an increased risk of fracture are the spine, hip, pelvis, wrist and upper arm. Although the WHO (1994) bases the diagnosis of osteoporosis on the presence of low-impact fractures or a measurement of BMD at least 2.5 standard deviations below the normal adult mean for white women (T score < –2.5), this does not give an accurate indication of overall bone strength. Furthermore, it is unclear how this criterion can be applied to men and children or to different ethnic groups (NIH Consensus Development Panel on Osteoporosis Prevention 2001). Thus, it has more recently been suggested that the diagnosis of osteoporosis should be based on a risk-based assessment rather than just on bone densitometry (Bonnick 2002; National Institute of Health 2000).

The deterioration that leads to osteoporosis occurs in both the cortical and trabecular bone. This results in a decreased mass of cortical bone and a decrease in the structural quality of the trabecular bone, giving it a porous appearance. This deterioration in bone quality is a result of imbalance in the activity of cells involved in the two processes of bone remodelling: formation of new bone (by osteoblasts) and resorption of old bone (by osteoclasts). Peak bone mass is approached before the age of 20 and is reached around the age of 30 (American Association of Clinical Endocrinologists 2001). If too little bone formation occurs before this period then the subsequent resorption of bone

that occurs with age may result in low bone density. Alternatively, low bone mass may be a result of bone resorption which occurs too rapidly. In addition, increased activation frequency results in an increase in bone turnover caused by increases in both formation and resorption, and is the cause of decreased bone mass in postmenopausal women.

A number of factors affecting bone remodelling can lead to the development of osteoporosis, including primary factors such as age, hormones, diet and lifestyle, and secondary causes such as thyroid, liver, kidney and bowel disease; as well as medications, including corticosteroids, anti-convulsants and some oral contraceptives. Osteoporosis is most commonly seen in postmenopausal women owing to a combination of age and decreased hormones levels.

Patients may present to a clinician after having sustained a low-impact fracture or with unexplained back pain. Alternatively, a patient may be suspected of being at risk of osteoporosis owing to age, menopausal status, or medication or disease history. Estimates of the number of Australians with osteoporosis vary widely depending on data sources. Mathers, Vos, and Stevenson (1999) estimated the incidence and prevalence of osteoporosis in 1996 to be 14,358 and 155,220 respectively using data from the 1995 National Health Survey. In comparison, Access Economics (Access Economics 2001) used data from the Australian Bureau of Statistics and the AIHW National Hospital Morbidity Database and expert advice to obtain a 1995 prevalence of osteoporosis of 1,788,700. This 10-fold discrepancy in the prevalence estimates of osteoporosis is most likely the result of the different methods used to obtain the estimates.

There are three long-term cohort studies examining the incidence of fracture in Australia: the Dubbo Osteoporosis Epidemiology Study (Jones et al 1994), the Geelong Osteoporosis Study (Sanders et al 1999) and the Tasmanian Older Adult Cohort study (Cooley & Jones 2001). These studies identified subjects who had suffered a fracture by reviewing radiology reports within the area. The subjects were aged ≥35 years in the Geelong study, ≥50 in the Tasmanian study and ≥60 in the Dubbo study. The results of these studies are summarised in Table 29. Estimates of the incidence of fractures in 2001 in Australians aged >60 years from the results of these studies lie between 51,000 and 73,000. Although these estimates are not restricted to those with low-impact (osteoporotic) fracture only, they are likely to be a reasonable estimate of the incidence of osteoporosis. Furthermore, as osteoporosis is a chronic condition, the prevalence is likely to be much higher than the incidence.

Table 29 Results of ongoing fracture studies

Study	DOES[a]	GOS[b]	TASOAC[c]
Age	≥ 60	≥ 35	≥ 50
Population of specified age group	3700	109900	229600
Number of fractures	306	2184	2010
Number of years	3.25	2	2
Lifetime fracture risk (women)	56%	42%	44%
Lifetime fracture risk (men)	29%	nr	27%
Total number of fractures in Australians >60 years in 2001 from study estimates	73000	51000	57000

Abbreviations: DOES, Dubbo Osteoporosis Epidemiology Study; GOS, Geelong Osteoporosis Study; nr, not reported; TASOAC, Tasmanian Older Adult Cohort.
[a] Jones et al (1994); [b] Sanders et al (1999); [c] Cooley and Jones (2001).

Conventional diagnosis and treatment

Diagnosis of osteoporosis or osteopenia

The measurement of BMD by DEXA is considered the gold standard for the diagnosis of osteoporosis. DEXA measures the mineral content of bone within a specific site, and a value for BMD is calculated by dividing the mineral content by the area of the site. BMD is measured in units of g/m^2. Although other sites can be measured to assess a person's fracture risk, for diagnostic purposes it is recommended that BMD be measured at the femoral neck, as this site has the greatest value in predicting both hip and other osteoporotic fractures (Marshall, Johnell, & Wedell 1996). In patients with osteoporosis, hip fracture is a common and severe occurrence following a fall. Note that BMD is accurate only when bone is fully mineralised. Therefore, osteomalacia, which results in decreased mineralisation, will lead to an underestimation of BMD (Kanis 2002).

At present, BMD testing using DEXA is listed on the Medicare Benefits Schedule (MBS) only for certain patient groups who are at high risk of osteoporosis (Sanders et al 1999). While it does include people who have suffered a low-impact fracture, it excludes postmenopausal women who have not suffered a fracture but who make up the largest fracture risk group.

Staging

The staging of bone mass in women (Table 30) is based on the thresholds set by the WHO and modified by the International Osteoporosis Foundation (Kanis & Glüer 2000; World Health Organization 1994). Although these categories are based primarily on female cohorts, there is evidence to suggest that a similar T-score can be used for the diagnosis of osteoporosis in men (Kanis & Glüer 2000).

The young adult female reference population represents peak bone mass and is taken from the National Health and Nutrition Examination Survey reference database comprising women in their twenties as the reference group. Because its distribution is approximately Gaussian normal, around 14.5 per cent of the reference population is considered osteopenic and approximately 0.5 per cent osteoporotic (Kanis 2002).

Table 30 Staging of bone mass in women

Category	T-score	Description
Normal	>–1	Hip BMD > 1 SD below young adult female reference mean
Osteopenia (low bone mass)	–1 to –2.5	Hip BMD > 1 SD below the young adult female mean but < 2.5 SD below this value
Osteoporosis	≤ –2.5	Hip BMD 2.5 SD or more below the young adult female mean
Severe osteoporosis	1 to –2.5 fragility fractures	Hip BMD 2.5 SD or more below the young adult female mean in the presence of one or more fragility fractures

Source: Kanis and Glüer (2000) and WHO (1994).

Assessment of fracture risk

Measurement of BMD is also used for prognosis to assess the risk of future fracture. Studies have shown that each 1 SD decrease in BMD approximately doubles the risk of fracture (Marshall, Johnell, & Wedell 1996). However, the values vary depending on the site measured; the highest gradient of risk for a specific site is seen when measured at that particular site. Therefore, the gradient of risk (after a decrease in BMD of 1 SD compared with the reference population) of forearm fracture is 1.7 (confidence interval: 1.4–2.0) when BMD is measured at the distal radius, for hip fracture is 2.6 (CI: 2.0–3.5) when measured at the femoral neck, and for vertebral fracture is 2.3 (CI: 1.9–2.8) when measured at the lumbar spine (Kanis 2002; Marshall, Johnell, & Wedell 1996). The positive predictive value of using BMD to predict fracture in women over 50 with a BMD in the osteoporotic range is approximately 45 per cent. However, the sensitivity is low; only 4 per cent of fractures in women over 50 occur in women with osteoporosis (Kanis et al 2001). The low sensitivity of using BMD to predict fracture risk is the reason why screening is not recommended in menopausal women (World Health Organization 1994).

Other methods can be used to assess fracture risk. These include determining the presence of risk factors such as previous low-impact fractures, hypogonadism, long-term use of corticosteroids, and previous or current metabolic, renal, hepatic or gastrointestinal disorders. Lifestyle factors such as poor calcium intake, smoking and alcohol consumption may also contribute (Kanis 2002).

Biochemical measurement of bone turnover using bone formation and resorption markers can also be used to assess fracture risk. The biochemical markers of bone turnover are summarised in Table 2. Studies in menopausal and older women show an association between bone turnover and fracture independent of BMD (Garnero et al 1996; Garnero et al 2000; Hansen et al 1991). Therefore, it has been suggested that a combination of BMD measurement and biochemical markers may be useful in predicting fracture risk.

Treatment

The aim of the assessment of fracture risk is to target treatments to those who are at the highest risk of fracture. The Australian Fracture Prevention Summit was held in 2001 (Sambrook et al 2002). One of its main aims was to develop evidence-based guidelines for the treatment of osteoporosis. The key recommendations regarding the treatment of osteoporosis are summarised in Table 31.

Table 31 Key recommendations regarding the treatment of osteoporosis in Australia

Patient group	Recommendation	Type of therapy	Adjunctive therapy
Postmenopausal women with osteoporosis (T < –2.5)	Treat to prevent (further) fracture	*First-line*	Calcium and vitamin D
		Alendronate or risendronate (spinal or non-spinal) or raloxifene (spinal only)	Intermittent PTH for very low BMD (when available)
		Second-line	
		Etidronate, HRT	
Postmenopausal women with osteopenia (T = –1 to 2.5)	Consider prevention of bone loss	HRT or raloxifene or alendronate or risendronate	–
Postmenopausal women with normal BMD (T > –1)	Consider repeat BMD in 2 years	None	–
Men with primary osteoporosis (T < –2.5)	Treat to prevent (further) fracture	Alendronate or etidronate	–
Men with hypogonadism	Treat to prevent (further) fracture	Testosterone replacement therapy	–
Postmenopausal women and older men receiving glucocorticoids	Prophylaxis to reduce fracture risk	*First-line*	Vitamin D
		Alendronate or risendronate or etidronate	

Abbreviations: BMD, bone mineral density; HRT, hormone replacement therapy; PTH, parathyroid hormone.
Source: Adapted from Sambrook et al (2002).

There has recently been some controversy regarding the use of drug regimes combining oestrogen and progesterone. In July, 2002, the *Journal of the American Medical Association* reported that a randomised, controlled trial of combination hormone replacement therapy (HRT) had been stopped early owing to concerns over health risks, which included a 26 per cent increased risk of breast cancer in women in the treatment arm of the study (Fletcher & Colditz 2002; Writing Group for the Women's Health Initiative Investigators 2002). The claims made in the study were reviewed by an expert group established by the Australian Drug Evaluation Committee so that appropriate action could be taken by the Therapeutic Goods Administration and information could be passed on to clinicians and consumers (Tattersall 2002). One conclusion reached by the expert committee was that 'the continued use of combined HRT for women with established osteoporosis is also an acceptable option for many, but women should discuss the benefits and risks with the prescribing doctor'. Therefore, as noted by Tattersall (2002), 'the benefit of a reduced fracture rate with long-term combined HRT must now be balanced against the increased risks of breast cancer, stroke, heart disease and thromboembolism' and that the 'relative efficacy and safety of HRT must be considered against that of other interventions, including ensuring adequate calcium intake and vitamin D status, exercise, or taking bisphosphonates or selective oestrogen-receptor modulators'.

Treatment monitoring

In addition to its use in the diagnosis of osteoporosis, bone densitometry is also used routinely to monitor patient responses to hormone replacement and anti-resorptive therapy. Although it is well established that a low baseline BMD is related to an increase in fracture risk, the relationship between treatment-induced increases in BMD and reductions in fracture risk is less clear (Bonnick 2002). A number of studies have shown a weak to moderate relationship with changes in BMD accounting for anywhere between 4 and 67 per cent of reduction in fracture risk. Two other studies have shown stronger associations (Cummings et al 2002; Marcus et al 2002)). One of a number of possibilities

is that changes in bone turnover might account for a substantial proportion of the decreased fracture risk. The suggestion therefore is that a change in bone marker levels may be sufficient to predict treatment effectiveness without the need to show that changes in bone marker are related to changes in BMD.

Owing to the precision error of the DEXA measurement (approximately 1%–3%) and the fact that the average bone loss rate is 0.5 to 2 per cent per year, while the average bone gain during therapy is 1 to 6 per cent over 3 years, changes in BMD during therapy can generally only be confidently shown after 1 to 2 years of therapy (Brown & Josse 2002). A further problem with the serial measurements of BMD to assess treatment response is regression to the mean. In a study of patients from two-treatment, randomised controlled trials, (Cummings et al 2000) showed that the BMD of patients during the second year of therapy had the tendency to 'regress' to the mean change of the whole group after the first year. In other words, patients who had an increase in BMD during the first year lost BMD during the second year, while patients who had a decrease in BMD during the first year gained BMD during the second year. Although Cummings concluded that this phenomenon negated the utility of DEXA to show changes in BMD, (Bonnick 2002) argues that this has no bearing on the consideration of results in the individual patient.

Although treatment for the prevention or minimisation of osteoporosis has been shown to be effective, this may be compromised by poor adherence and persistence with these long-term therapies. It has been suggested that biochemical markers of bone turnover may be useful in improving patient compliance, and thus that they may improve the efficacy of these treatments. However, as yet there is little evidence for this. One recent abstract has addressed this issue using the bone resorption marker NTx (n-terminal telopeptide) (Clowes, Peel, & Eastell 2002). The results of this study suggest that monitoring therapy (both by nurses and by using NTx) may improve persistence and adherence to treatment over 1 year than patients not monitored. However, although results for the group monitored by nurses were statistically significant, the results of the group monitored using NTx were not.

Potential value of Ostase

This review examines the potential role of Ostase in (i) predicting fracture risk, and (ii) monitoring therapy in patients suspected of having, or having a diagnosis of, osteoporosis. These roles are illustrated in the clinical flow chart in Appendix F. After consultation with the expert panel convened for this review it was agreed that Ostase would most likely be used in the following ways in patients with, or at risk of, osteoporosis:

- For the evaluation of fracture risk – Ostase may be used in conjunction with BMD testing in order to aid treatment decisions. For example, a patient with a BMD in the osteopenic range (T score between –2.5 and –1) may benefit from preventive treatment if Ostase shows that bone turnover is high (see flow chart in Appendix F).

- For the monitoring of treatment to prevent or minimise osteoporosis – It has been suggested that measuring bone markers after 3 to 6 months of treatment may be able to predict increases in bone density (which are thought to be associated with a decreased fracture risk), not generally detectable until 1 to 2

years after treatment begins (owing to the precision error). Although Ostase is unlikely to replace BMD testing, it may allow clinicians to intervene at an earlier stage if treatment is not proving to be effective. Alternatively, it has been suggested that changes in bone turnover themselves may predict long-term reductions in fracture risk.

A number of reviews have outlined the potential use of biochemical markers of bone turnover in the assessment and monitoring of osteoporosis (for example see Miller et al (1999), Delmas et al (2000a), Fairweather-Tait (2002) and Fournier et al (1998)). Most recently, the Scientific Advisory Council of the Osteoporosis Society of Canada (Brown & Josse 2002) reviewed the evidence pertaining to the diagnosis and management of osteoporosis in Canada for their clinical guidelines. They came to the following conclusion regarding the use of biochemical markers in predicting fracture risk and monitoring treatment in patients with osteoporosis:

> 'Bone turnover markers should not yet be used for routine clinical management. Additional studies are needed to confirm their use in individual patients. However, with refinement of assay technology and better understanding of biological variability, we believe they will become a useful adjunct for risk assessment and management.'

With regards specifically to treatment monitoring, a recent paper by Chapurlat and Cummings (2002) describes a decision-analytic model which examines the potential value of monitoring antiresorptive therapy by using early measurement of a resorption marker. The authors conclude that the 'follow-up of osteoporotic women treated with a second-generation bisphosphonate during a 5-year period using an early measurement of a serum marker of bone resorption may increase effectiveness of the treatment on quality of life, but the effect is very small.' It is important to note that while this suggests that there may be a small benefit in monitoring antiresorptive therapy with a bone resorption marker, this does not necessarily imply that monitoring therapy using a bone formation marker, such as BALP as measured by Ostase, will be beneficial.

Review of the literature search

Search strategy

The search strategies used to identify relevant studies for osteoporosis are outlined in the Approach to Assessment section (page 7).

Eligibility criteria

The eligibility criteria used to evaluate abstracts and full papers are shown in Table 32. These criteria relate to the study question as summarised in Appendix E.

For osteoporosis, Ostase is to be used in addition to the measurement of BMD by DEXA to assess fracture risk and to monitor hormone replacement and antiresorptive therapy. Therefore, to be indicated for MBS reimbursement of Ostase, patients would also have to be indicated for reimbursement of DEXA. Currently, the listing of DEXA on the MBS does not include peri- and postmenopausal women who have not experienced a low-impact fracture. As this group could potentially benefit the most from having their fracture risk determined they would be included in the analysis. However, the listing of DEXA on the MBS is currently under review. Groups of patients who may

potentially benefit from BMD testing are thought to be those over the age of 65 and those with a family history of osteoporosis (Cummings et al 1995).

Table 32 Eligibility criteria for osteoporosis

Patients	1. Perimenopausal and postmenopausal women, who make up the largest risk group for osteoporosis. 2. As Ostase is to be used in addition to BMD testing by DEXA, patient groups eligible for bone densitometry testing on the MBS will be eligible for inclusion also. The current indications for DEXA on the MBS include the following: A. For the confirmation of a presumptive diagnosis of low BMD[a] made on the basis of: i) one or more fractures occurring after minimal trauma ii) monitoring of low BMD proven by previous bone densitometry. B. For the diagnosis and monitoring of bone loss associated with one or more of the following conditions: ▪ prolonged glucocorticoid therapy[b] ▪ conditions associated with excess glucocorticoid ▪ male hypogonadism[c] ▪ female hypogonadism lasting more than 6 months before the age of 45[d] ▪ primary hyperparathyroidism ▪ chronic liver disease ▪ chronic renal disease ▪ proven malabsorptive disorders[e] ▪ rheumatoid arthritis ▪ conditions associated with thyroxine excess. C. For the measurement of bone density 12 months following a significant change in therapy for established low BMD; or the confirmation of a presumptive diagnosis of low BMD made on the basis of one or more fractures occurring after minimal trauma.
Intervention	Articles were excluded if none of the Ostase tests (Tandem-R, Tandem-MP or Access Ostase) was used to measure BALP.
Comparator	Ostase is to be used in addition to BMD testing by DEXA. Therefore, the study had to include measurement of BMD by DEXA.
Outcome	The study had to assess the use of Ostase in predicting fracture risk or monitoring treatment. *Diagnostic accuracy:* The study had to include at least one of the standard diagnostic outcomes (sensitivity, specificity, PPV or NPV), present a relative risk or odds ratio, or present results of a regression analysis of the association between Ostase and fracture or BMD. Studies which showed only changes in Ostase levels after treatment were excluded. Studies which presented only simple correlations between Ostase and fracture or BMD were noted but were not included in the analysis. *Change in management and patient outcomes*
Other	Papers were excluded if fewer than 10 patients were reported on. The exception to this may be in the situation where there are no publications with more than 10 patients. Rather than excluding all papers for a clinical indication on the basis of this criterion, available information is reported, noting limitations. Review-only / editorial / technical papers were excluded. Data available in abstract form only were excluded. All non-English papers were excluded. Papers which report no clinical results were be excluded.

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

[a] Low BMD is defined as a Z-score of <–1.5 (based on age-matched mean at the same site and in the same sex or a T-score of <–2.5 (based on the young normal mean at the same site and in the same sex).

[b] A dosage of inhaled glucocorticoid equivalent to or greater than 800 µg beclomethasone or budesonide per day or a supraphysiological glucocorticoid dosage equivalent to or greater than 7.5 mg prednisolone taken orally per day by an adult for a period anticipated to last for at least 4 months.

[c] Serum testosterone levels below the age-matched normal range.

[d] Serum oestrogen levels below the age-matched normal range.

[e] Malabsorption of fat (faecal fat estimated at >18 g / 72 h on a normal fat diet); or bowel disease with presumptive vitamin D malabsorption (subnormal circulating 25-hydroxy vitamin D); or histologically proven coeliac disease.

Results

The search of databases and Web sites of international health technology assessment agencies identified two reviews that examined the utility of bone markers (including BALP) in predicting fracture risk and monitoring of treatment (Nelson et al 2001, Smith and Greer 2001). These are summarised in Table 52.

The search of electronic databases identified 2520 non-duplicate citations relating to osteoporosis.

Of the 2520 citations, 2049 were excluded after review of the titles and abstracts. Full copies of the remaining 471 articles were retrieved and a further 447 were excluded.

In total, 460 citations were excluded on the basis of patient group, 1026 studies (1028 citations) on intervention, 1004 studies (1008 citations) on other criteria.

There were 24 studies potentially eligible for inclusion in the review. They are summarised in Table 50 and Table 51 in Appendix C. A further 11 studies were excluded, as they presented only simple correlation coefficients (r) as a measure of an association between BALP and fracture or BMD. A simple correlation assumes that there is no dependency between two variables and gives an indication of the intensity of an association between two variables. However, it does not give a measure of the magnitude of the association (ie, the quantitative change of one variable with respect to another). Thus, a simple correlation coefficient does not provide an indication of predictive ability. On the other hand, simple and multiple regression analyses assume that there is a dependency between the two variables being measured and offer the coefficients of determination statistics (r^2 and R^2 respectively). The coefficients of determination can be interpreted as the percentage of the total variation in Y (eg, fracture or BMD) that is explained or accounted for by the variation or change in X (eg, BALP). As this review is examining the relationship between two variables which are assumed to be dependent (ie, fracture or BMD dependent on the rate of bone turnover), studies presenting only the results of simple correlations between BALP and fracture or BMD were excluded from the analysis (Zar 1999). However, a list of these studies and the results of their correlation analyses is included in Appendix D. The correlation results for the included studies are discussed in the report, and are presented in the tables in Appendix C.

Thirteen studies were identified which address the clinical questions examined for osteoporosis (Table 33).

Table 33 Osteoporosis publications

Clinical question or citation	Study type	NHMRC level of evidence
Assessment of fracture risk		
Ross et al (2000)	Case series (cohort subgroup)	IV
Garnero et al (2000)	Case series (cohort subgroup)	IV
Garnero et al (1996)	Nested case-control	III-2
Garnero et al (1999)	Case series (cohort subgroup)	IV
Bauer et al (1999)	Case series (cohort subgroup)	IV
Chapurlat et al (2000)	Case series (cohort subgroup)	IV
Cosman et al (1996)	Case series	IV
Treatment monitoring		
Bjarnason et al (2001)	Case series (RCT subgroup)	IV
Bjarnason et al (2000)	Case series (RCT subgroup)	IV
Garnero (1999)	Case series (RCT subgroup)	IV
Dresner-Pollak (2000)	Case series (RCT subgroup)	IV
Delmas et al (2000b)	Case series (2 RCTs subgroup)	IV
Marcus et al (1999)	Case series (RCT subgroup)	IV

Abbreviation: RCT, randomised controlled trial.

Methodological issues in the studies

As outlined in Appendix G, several factors may compromise a study's validity, and therefore limit the extent to which the results can be generalised to clinical scenarios.

The 13 studies that form the basis of the review of this indication were generally of poor methodological quality. The following methodological issues limited our ability to evaluate the data reported by the studies included in this review:

- *Potential for selection bias:* The methods used to select patients into studies were often poorly described. Therefore, it is difficult to determine the extent to which patient selection may have affected the study results.

- *Generalisability:* Patients with comorbidities known to influence bone metabolism were excluded from study samples. This may limit the extent to which results can be generalised to clinical populations.

- *Poor follow-up:* In many of the studies either follow-up was poor or not all patients were included in the analysis. In addition, outcomes were sometimes not measured in some patients. It was often unclear how many patients were included in the analyses. Therefore, the results may not reflect the results of the original population.

- *Lack of validation of models:* A number of studies used multivariate analysis to derive a diagnostic model. However, these were not subsequently validated in other samples or populations (Knottnerus & Muris 2002).

- Many studies report the results of the population as a whole, giving associations between BALP and fracture or BMD as odds ratios, relative risks or correlations, related only to groups, rather than individual patients. The description of group differences does not necessarily allow the results of a study to be applied to an individual.

In addition to the specific problems outlined above, diagnostic test studies are often poorly reported. Thus, it can be difficult to be certain of study quality. The specific quality characteristics of each included study are summarised in the following section.

Diagnostic accuracy of Ostase

Prediction of fracture risk

Seven studies were identified which examined the utility of bone markers (including BALP by Ostase) in predicting the future risk of fracture or low BMD (Bauer et al 1999; Chapurlat et al 2000; Cosman et al 1996; Garnero et al 1996; Garnero et al 1999; Garnero et al 2000; Ross et al 2000). All studies included peri- or postmenopausal women who were not yet diagnosed with osteoporosis. Some studies included premenopausal women as a control group. Definitions of peri- and postmenopausal women were as shown in Table 34.

Table 34 Definitions of menopausal status

Study	Postmenopausal	Perimenopausal	Premenopausal
Ross et al (2000)	Not defined	Not defined	–
Garnero et al (2000)	Absence of menses ≥ 6 months	–	–
Garnero et al (1996)	Aged ≥ 75 years	–	Regular menses and without disease or drugs known to influence calcium metabolism, including the oral contraceptive pill (control population)
Garnero et al (1999)	Absence of menses ≥ 12 months	–	–
Bauer et al (1999)	Aged ≥ 65 years	–	–
Chapurlat et al (2000)	1-year cessation of menses	FSH ≥ 16.7 IU/L and/or irregular menses (>35-day cycles after previously regular cycles)	Cycling regularly (25–35 days/cycle) with FSH levels < 16.7 IU/L
Cosman et al (1996)	> 1 year since last menstrual period and FSH level (not defined)	–	Not defined.

Abbreviations: FSH, follicle-stimulating hormone.

Six of the seven studies included a subgroup of women from the Hawaii Osteoporosis Study (HOS), the OFELY study (Chapurlat et al 2000; Garnero et al 1999; Garnero et al 2000), the EPIDOS study (Garnero et al 1996) and the Study of Osteoporotic Fractures (SOF) (Chapurlat et al 2000). One study used cases from their menopause clinic (Cosman et al 1996). Studies examined the utility of a number of different markers of bone turnover for predicting fracture risk. However, only the data relating to the measurement of BALP by Ostase are included in this review. Three studies used fracture as the outcome (Garnero et al 1996; Garnero et al 2000; Ross et al 2000). The remaining four used BMD measured by DEXA as a surrogate for fracture outcome (Bauer et al 1999; Chapurlat et al 2000; Cosman et al 1996; Garnero et al 1999).

Various statistical methods were used to measure the ability of bone markers to predict fracture risk or low BMD. These include diagnostic accuracy, risk as measured by relative risk and odds ratio, and regression analysis.

Table 35 and Table 36 summarise the main characteristics and quality of these studies.

Table 35 Study characteristics – predicting fracture risk in peri/postmenopausal women without osteoporosis

Study	Study type	Aim, follow-up	Population	*N*	Bone marker tests	Reference standard	Outcomes
Ross et al (2000)	Cohort subgroup (HOS)	Fracture risk Mean follow-up 2.7 years	Community-dwelling postmenopausal women	512	BALP (Ostase); urine CTx	Fracture (spine or non-spine)	Associations of bone markers and calcaneus BMD with fractures (odds ratios); multiple logistic regression analysis
Garnero et al (2000)	Cohort subgroup (OFELY)	Fracture risk Mean follow-up 5 years	Healthy postmenopausal women	435	BALP (Ostase); OC; serum CTx; PICP; PINP; Dpy; NTx; urine CTx	Fracture (peripheral or spinal)	Relative risk of osteoporotic fracture in women with elevated bone marker levels (4th quartile and >2 SD).
Garnero et al (1996)	Retrospective nested case-control (EPIDOS)	Fracture risk Mean follow-up 22 months	Healthy older (>75) postmenopausal women	401	BALP (Ostase); OC; CTx; NTx; Dpy	Fracture (hip) BMD (femoral neck)	Bone markers and BMD as predictors of hip fracture (odds ratio); correlation between marker levels and BMD
Garnero et al (1999)	Cohort subgroup (OFELY)	Fracture risk 4 year follow-up	Postmenopausal women	305	BALP (Ostase); OC; PICP; PINP; serum CTx; urine CTx; NTx	BMD (radius)	Prediction of bone loss by bone markers (sensitivity, specificity, PPV, NPV, odds ratio); correlation
Bauer et al (1999)	Cohort subgroup (SOF)	Fracture risk Mean follow-up 3.8 years	Women >65 years of age	412	BALP (Ostase); OC; NTx; urine CTx; Dpy; Pyr	BMD (total hip and 3 subregions)	Identification of women in highest tertile and above median for bone loss using bone markers (sensitivity, specificity, PPV NPV); correlation
Chapurlat et al (2000)	Cohort subgroup (OFELY)	Fracture risk 3-year follow-up	Pre- and perimenopausal women	320	BALP (Ostase); OC; PICP; NTx; CTx	BMD (whole body, spine, hip and radius)	Prediction of BMD by baseline markers (correlation)
Cosman et al (1996)	Case series	Fracture risk 3-year follow-up	Premenopausal and treated and untreated postmenopausal women	81	BALP (Ostase); OC; PICP; TALP; TRAP; ICTP; Hyd; Ca; Pyr; Dpy	BMD (lumbar spine and femoral neck)	Multiple regression in untreated postmenopausal women (*n* = 30)

Abbreviations: BALP, bone alkaline phosphatase; Ca, calcium; Dpy, deoxypyridinoline; CTx, c-terminal telopeptide; HOS, Hawaii Osteoporosis Study; Hyp hydroxyproline; ICTP, carboxy propeptide of type 1 collagen; NPV, negative predictive value; OC, osteocalcin; NTx, n-terminal telopeptide; PICP, c-terminal propeptide of type I collagen; PINP, n-terminal propeptide of type I collagen; PPV, positive predictive value; Pyr, pyridinoline; SOF, Study of Osteoporotic Fractures; TALP, total alkaline phosphatase; TRAP, tartrate-resistant acid phosphatase.

Table 36 Quality of studies examining prediction of fracture risk

Study	Selection bias minimised?	Follow-up sufficient?	Measurement bias minimised?	Confounding avoided?	Statistical analysis appropriate?	Comments
Ross et al (2000)	Unclear. The 1105 women who originally participated had a more frequent history of taking hormones, were younger and had lower systolic blood pressure than the 28% of the original target population who chose not to participate (Heilbrun et al 1991). Only 721/1105 were available for this study.	Yes. 512/721 had urine and serum samples available. Baseline characteristics similar for women with/without baseline samples.	Yes. Fracture is the outcome. BALP, BMD and fracture measured independently and in all patients.	Yes. BMD adjusted for subject age and BALP adjusted for age and sample collection time (relates primarily to CTx). In multiple regression analysis, adjustments were made for a variety of physical frailty measures.	Unclear. Odds ratios were obtained from logistic regression analysis. No cut-off values given for BALP or BMD.	May have been subject to some selection bias as only 45% of the original target population were available for this analysis. Potential confounders were thoroughly investigated.
Garnero et al (2000)	Unclear. No details of random selection reported for the OFELY study. Only 18% of women contacted volunteered for the study. Education levels higher for women in the subgroup than French population.	No. Only 79% of 435 women had follow-up X-rays. Therefore, non-symptomatic vertebral fracture incidence may be unreliable.	Yes. Fracture is the outcome. BALP and fracture measured independently. BALP measured independently of other tests. BALP and fracture assessed in same patients.	Yes. Information regarding potential confounders was collected at baseline and analyses were adjusted for baseline BMI, age, prevalent fractures and physical activity. It is unclear whether treatment was initiated in any women in response to test results.	Yes. Logistic regression used to analyse relation between baseline bone markers and hormones and the risk of fracture. T-score cut-offs calculated from pre-menopausal population of OFELY study.	There is the potential for significant selection bias given the low number of women participating and the poor follow-up for vertebral fractures.
Garnero et al (1996)	Unclear. Women from EPIDOS cohort. No detail on number of women volunteering compared with number invited to take part. No comparison of cohort to wider population.	Yes. Nested case-control, so 100% follow-up.	Yes. Fracture is outcome and measured independently from BALP.	Yes. Cases and controls were matched by age and time of recruitment. Adjusted for factors such as gait speed and femoral neck BMD.	Yes. Odds ratios were obtained from conditional logistic regression on matched sets to take into account design of study. Marker cut-offs not reported for highest quartile but 1 SD increase and upper limit of premenopausal range can be calculated from values provided as baseline.	There may be some potential for selection bias, but hip fracture is unlikely to have been underestimated.
Garnero et al (1999)	Unclear. Women taken from OFELY study. See Garnero et al (2000).	Unclear. 11% of potentially eligible women withdrew from the study owing to personal reasons – this is not explained.	Yes. BMD is the outcome and is measured independently and at a separate time from BALP.	Analyses adjusted for age only.	Yes. Calculated annual percentage change of BMD as outcome, and 97% of women had 4 values at baseline, and 2, 3 and 4 years. Linear regression used to assess relationships – bone marker data log-transformed. Marker cut-off calculated as T score > 2. Not provided but can be calculated from original paper.	It is difficult to rule out the potential for selection bias to occur owing to low percentage of women participating in study and poor description of study drop-outs.

Study	Selection bias minimised?	Follow-up sufficient?	Measurement bias minimised?	Confounding avoided?	Statistical analysis appropriate?	Comments
Bauer et al (1999)	Unclear. Study included a subgroup of the SOF study. SOF recruited women from 4 regions in the US. Women selected from a combination of HMOs, jury records and existing studies. No details on how women were selected or how many agreed to participate. Bauer study included only 295 of 9703 women in SOF study.	No. 77% of 412 women had a follow-up DEXA: 31 died, 4 lost to follow-up and 82 did not undergo second DEXA. No reason given for failure to undergo follow-up DEXA.	Yes. BMD is the outcome and is measured independently from BALP.	Analyses adjusted for age only.	Yes. Calculated sensitivity, specificity, NPV and PPV. Marker cut-off levels are reported.	Cannot rule out selection bias owing to poor reporting of patient selection, and number of women not undergoing BMD testing at endpoint (20%).
Chapurlat et al (2000)	Unclear. Includes a subgroup of pre- and perimenopausal women from the OFELY study. Potential problems outlined above.	No. 196/272 had BMD measured over 3 years. 11% lost to follow-up. Analysis of relation between bone loss and markers includes only perimenopausal women with increased FSH (*n* = 59).	Yes. BMD is the outcome and is measured independently from BALP.	Not reported.	Yes. Bonferroni adjustments for multiple comparisons made where appropriate. No cut-offs reported.	Cannot rule out selection bias (see above regarding OFELY study). Analysis included only perimenopausal women with increased FSH. Potential confounders not adjusted for.
Cosman et al (1996)	Unclear. Not reported whether series was consecutive or selected.	No. Full biochemical measurements were available for only 30/40 (75%) of untreated postmenopausal women.	Yes. BMD is the outcome and is measured independently from BALP.	Not reported.	Number of patients too low compared with number of independent variables in regression analysis.	Cannot rule out selection bias owing to poor reporting of patient selection and number of women not undergoing biochemical testing. Also, inappropriate statistical analysis.

Abbreviations: BALP, bone alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; CTx, c-terminal telopeptide; DEXA, dual X-ray absorptiometry; FSH, follicle-stimulating hormone; HMO, health maintenance organisation; NPV, negative predictive value; PPV, positive predictive value; SOF, Study of Osteoporotic Fractures.

Predicting fracture risk using fracture as the outcome

The results of most of the studies included in this section had significant potential to be affected by various biases, as outlined in Table 36. Therefore, this should be taken into account when assessing the results of the studies. Of the seven studies examining the use of biochemical bone markers (including Ostase) to assess fracture risk, three used fracture as the outcome (Garnero et al 1996; Garnero et al 2000; Ross et al 2000).

- The study by Ross et al (2000) (n = 512) aimed to assess the ability of markers of bone turnover (BALP and CTx [c-terminal telopeptide]) as well as calcaneus BMD to identify an increased risk of osteoporotic fracture in postmenopausal women. Women included in this study comprised a subgroup of women from HOS (Heilbrun et al 1991). The results of this study suggest that BALP as measured by Ostase was significantly associated with both spine and non-spine fractures when either adjusted or unadjusted for calcaneus BMD with odds ratios ranging from 1.45 to 1.88. These were similar to the age-adjusted odds ratios for calcaneus BMD alone. When entered in a logistic regression model, BALP as measured by Ostase was shown to be an independent predictor of fracture (P = 0.017). When a hierarchical logistic regression model was used, the incremental contribution of BALP to BMD for predicting fracture was significant (P = 0.0009). In addition, the likelihood test statistic (G) showed that the contribution of BALP to the model was comparable to that of BMD alone. The authors reported that similar odds ratio results were seen for CTx, but the addition of CTx to the model containing BMD and BALP did not provide additional statistical power. The authors concluded that bone turnover assessed by biochemical markers (BALP using Ostase and CTx) is significantly associated with increased fracture risk. They also note that combining BALP and CTx did not improve the association with fracture risk, compared with measurement of markers individually.

- The study by Garnero et al (2000) (n = 435) examines the utility of bone markers in predicting spinal and peripheral osteoporotic fracture in a subgroup of women from the OFELY study. The results (Table 37) suggest that different cut-offs of BALP may significantly predict the risk of fracture after adjustment for various other variables, with statistically significant relative risks varying from 1.9 to 2.5. The exception to this was the ability of the highest quartile of BALP to predict fracture in women who had no prevalent fracture at baseline (after adjustment for age and physical activity), which was of borderline significance (P = 0.07). Note that this is the patient group most likely to benefit from the assessment of fracture risk. The authors concluded that a high level of BALP (among other markers and factors) was associated with increased risk of osteoporotic fracture in postmenopausal women. However, this conclusion should be interpreted with caution in light of some of the methodological limitations outlined, including the potential for selection bias and the poor follow-up of vertebral fracture.

- The study by Garnero et al (1996) (n = 401) examines the utility of bone markers in predicting osteoporotic hip fracture in older women taken from the EPIDOS study. High levels of BALP as measured by Ostase did not predict hip fracture. Odds ratios ranged between 0.9 and 1.1 and were statistically non-significant. The authors concluded that of all the bone markers studied only the resorption markers CTx and free deoxypyridinoline, in combination with hip BMD, proved useful in predicting risk of hip fracture in older women. Note that this study includes only women aged greater than 75 years, so the results may be generalisable only to this specific group.

Table 37 Summary of results – utility of Ostase in predicting fracture using fracture as the outcome

Trial	Marker	Outcome	RR (95% CI)	*P* value	OR (95% CI)	*P* value	Probability estimates (%)
	BALP	**Fracture**					
Ross et al (2000)	**Baseline**	**Mean follow-up 2.7 years**					
	BMD unadjusted	Spine			1.54 (1.12, 2.12)[a]		
	BMD adjusted	Spine			1.49 (1.07, 2.07)		
	BMD unadjusted	Non-spine			1.88 (1.34, 2.65)		
	BMD adjusted	Non-spine			1.80 (1.27, 2.56)		
	BMD unadjusted	Spine and non-spine			1.53 (1.18, 1.98)		
	BMD adjusted	Spine and non-spine			1.45 (1.11, 1.89)		
	BALP Z = 2 (BMD Z = –2, –1, 0, 1, 2)	Spine and non-spine					33, 24, 17, 12, 8
	BALP Z = 1 (BMD Z = –2, –1, 0, 1, 2)	Spine and non-spine					26, 19, 13, 9, 6
	BALP Z = 0 (BMD Z = –2, –1, 0, 1, 2)	Spine and non-spine					20, 14, 9, 6, 4
	BALP Z = –1 (BMD Z = –2, –1, 0, 1, 2)	Spine and non-spine					15, 11, 9, 5, 3
	BALP Z = –2 (BMD Z = –2, –1, 0, 1, 2)	Spine and non-spine					11, 8, 5, 3, 2
Garnero et al (2000)	**Baseline**	**Mean follow-up 5 years**					
	Cut-off (4th quartile)	All	2.4 (1.3, 4.2) [c]	0.005			
	Cut-off (T-score ≥ 2; 14.1 µg/L[b])	All	1.9 (1.1, 3.4) [c]	0.03			
	Cut-off (4th quartile)	All	1.9 (0.95, 2.7)[d]	0.07			
	Cut-off (4th quartile) Model 1	All	1.9 (1.0, 3.4) [e]	0.04			
	Cut-off (4th quartile) Model 2	All	2.1 (1.1, 3.8) [f]	0.02			
	Cut-off (4th quartile)	Non-vertebral and symptomatic vertebral	2.5 (1.3, 4.7) [c]	0.004			
	Cut-off (4th quartile)	Non-vertebral	2.4 (1.1, 4.9) [c]	0.03			
Garnero et al (1996)	**Baseline**	**Mean follow-up 22 months**					
	1 SD increase (continuous)	Hip			0.9 (0.8, 1.2)	NS	
	Cut-off (4th quartile)	Hip			0.9 (0.6, 1.4)	NS	
	Cut-off (*T*-score ≥ 2)	Hip			1.1 (0.7, 1.7)	NS	

Abbreviations: BALP, bone alkaline phosphatase; NS, not significant; OR, odds ratio; RR, relative risk; SD, standard deviation.

[a] All adjusted for age and time of sample collection; [b] calculated from premenopausal values in Garnero et al (1996); [c] Adjusted for age, prevalent osteoporotic fracture and physical activity; [d] adjusted for age and physical activity and excluding women with prevalent fracture; [e] adjusted for [c] and femoral neck BMD; [f] Adjusted for [c] and other hormones.

Predicting fracture risk using BMD as a surrogate outcome

Four studies used BMD (as measured by DEXA) as a surrogate outcome for fracture (Bauer et al 1999; Chapurlat et al 2000; Cosman et al 1996; Garnero et al 1999).

The study by Garnero et al (1999) (n = 305) examined the utility of bone markers in predicting the rate of change of BMD in the forearm and includes women from the OFELY study. A BALP cut-off level of T-score ≥ 2 had poor diagnostic accuracy to detect women with a rate of loss of mid and distal radius BMD in the highest tertile. In addition, the analysis of risk prediction using the odds ratio (OR) was not significant for distal radius BMD and was of borderline significance for mid-radius BMD. Although the authors concluded that 'increased levels of some of the biochemical markers of bone turnover are associated with greater radial bone loss', this does not include BALP.

Bauer et al (1999) (n = 412) examined the utility of bone markers in predicting hip bone loss in women over 65 years of age who had not used HRT. The participants included in this study are part of the larger Study of Osteoporotic Fractures (SOF). The results of the analysis show that using a high cut-off for BALP (either above median or highest quartile) was a poor predictor for women who lost >1.1 per cent total hip BMD per year (ie, the highest tertile), as shown in Table 38. The authors concluded that BALP and other biochemical markers 'have limited value for predicting rapid hip bone loss in individuals.'

Chapurlat et al (2000) (n = 320) examined the presence and magnitude of bone loss in pre- and perimenopausal women, and the relationship between hormone status and BMD. In this study, bone markers were used to identify women with high bone turnover. In a multiple regression analysis, baseline BALP and oestrogen (E_2) levels were found to be the two main determinants of bone loss at the femoral neck, accounting for 44 per cent of the variance in BMD (r^2 = 0.44, P = 0.016).

Cosman et al (1996) (n = 81) aimed to determine whether bone markers could be used to predict individual rates of bone loss. Premenopausal and treated and untreated postmenopausal women were included in the study and were recruited from a local clinic between 1988 and 1990. In 30 / 40 untreated postmenopausal women, a stepwise multiple regression analysis was performed including baseline and demographic variables as well as bone markers in order to predict the percentage rate of change of BMD in the spine and femoral neck. BALP, Hyp, ICTP and calcium intake were all independent predictors of bone loss. In combination they were able to predict 42 per cent of the variance in change in spine BMD. BALP was not an independent predictor of femoral neck BMD. Note that 15 of 40 women in the untreated menopausal group met the WHO criteria for osteoporosis. The authors concluded that 'measuring individual serum and urine markers of bone turnover cannot accurately predict bone loss rates in the spine and hip; however, combinations of demographic and biochemical variables could predict some of the variance in untreated postmenopausal women'.

Table 38 Summary of results – utility of Ostase in BMD as a surrogate outcome for reduction of fracture risk

Trial	Marker	Outcome	Sensitivity	Specificity	PPV	NPV	OR (95% CI)	Regression analysis
	BALP	BMD	%	%	%	%		R^2
Garnero et al (1999)	**Baseline**	**Follow-up 4 years**						
	Cut-off (T score ≥ 2)	Mid-radius cut-off rate of loss (3rd tertile)	39	79	48	71	1.8 (1.0, 3.2)	
	Cut-off (T score ≥ 2)	Distal radius cut-off rate of loss (3rd tertile)	36	77	44	71	1.61 (0.9, 2.8)	
Bauer et al (1999)	**Baseline**	**Mean follow-up 3.8 years**						
	Cut-off >11.6 ng/mL (median)	Total hip cut-off (highest tertile)[a]	59	46	35	69		
	Cut-off >15.0 (4th quartile)	Total hip cut-off (highest tertile)[a]	29	74	36	68		
Chapurlat et al (2000)	**Baseline**	**Follow-up 3 years**						
	Level + E_2 level	Femoral neck rate of loss						–0.442
Cosman et al (1996)	**Baseline**	**Follow-up 3 years**						0.15
	Hyp	Percentage rate of change spine BMD						0.24
	ICTP							0.35
	BALP							0.42
	Ca intake							

Abbreviations: BALP, bone alkaline phosphatase; BMD, bone mineral density; Hyp, hydroxyproline; ICTP, carboxy terminal propeptide of type I collagen; NPV, negative predictive value; NS, not significant; OR, odds ratio; PPV, positive predictive value.

[a] >1.1% of total hip BMD per year.

Treatment monitoring

Six studies were identified which examined the utility of bone markers (including BALP) in predicting response to treatment. All studies used cohorts of women included in randomised controlled trials of the following therapies: (i) HRT used in non-osteoporotic postmenopausal women (Bjarnason & Christiansen 2000; Delmas et al 2000b; Dresner-Pollak 2000; Marcus et al 1999), and (ii) raloxifene and (iii) alendronate used in osteoporotic postmenopausal women (Bjarnason et al 2001; Garnero 1999). Five of the six studies examined a number of different bone markers including BALP measured by Ostase, but the study by Dresner-Pollak et al (2000) examined BALP only.

The main characteristics of the studies included in this section are shown in Table 39 and Table 40, and the main quality characteristics are shown in Table 41 and Table 42. These tables highlight that many of the studies evaluated in this section of the review had a variety of methodological biases.

Table 39 Study characteristics – monitoring treatment to prevent osteoporosis in peri/postmenopausal women without osteoporosis

Study	Study type	Aim, follow-up	Population	*N*	Bone marker tests	Reference standard	Outcomes
Bjarnason and Christiansen (2000)	Cohort / RCT	Treatment monitoring – HRT	Early postmenopausal women	153	BALP (Ostase); OC; urine CTx; serum CTx	BMD (lumbar spine and left femur)	Accuracy of bone markers to predict response to treatment (sensitivity, PPV, NPV, ROC curves); correlations.
Dresner-Pollak (2000)	Cohort / RCT (Menopause Clinic, Israel)	Treatment monitoring – HRT 2-year follow-up	Postmenopausal women	90	BALP (Ostase)	BMD (lumbar spine and femoral neck)	Prediction of BMD by short-term change in BALP (sensitivity, specificity, PPV, NPV, AUC)
Delmas et al (2000b)	Cohort / 2 RCTs	Treatment monitoring – HRT 2-year follow-up	Postmenopausal women	569	BALP (Ostase); OC; S CTx; urine CTx	BMD (lumbar spine)	Accuracy of bone markers to predict response to treatment (sensitivity, PPV, ROC curves); logistic regression; correlation
Marcus et al (1999)	Cohort / subgroup of RCT (PEPI)	Treatment monitoring – HRT 3-year follow-up	Postmenopausal women (< 10 years)	293	BALP (Ostase); BALP (Alkphase-B); CTx; NTx; Pyr; Dpy	BMD (lumbar spine and hip)	Relationship of bone markers to 1- and 3-year BMD change (correlations, regression analysis); relationship of baseline and % change markers to BMD change (correlations, regression analysis)

Abbreviations: AUC, area under the curve; BALP, bone alkaline phosphatase; Ca, calcium; CTx, c-terminal telopeptide; Dpy, deoxypyridinoline; NPV, negative predictive value; NTx, n-terminal telopeptide; OC, osteocalcin; PICP, c-terminal propeptide of type I collagen; PEPI, Postmenopausal Estrogen / Progestin Interventions trial; PPV, positive predictive value; Pyr, pyridinoline; ROC, receiver operator characteristic; RCT, randomised controlled trial; SOF, Study of Osteoporotic Fractures.

Table 40 Study characteristics – monitoring treatment for osteoporosis in postmenopausal women

Study	Study type	Aim, follow-up	Population	*N*	Bone marker tests	Reference standard	Relevant outcomes
Bjarnason et al (2001)	RCT subgroup (MORE)	Treatment monitoring – raloxifene 3 years	Postmenopausal women with osteoporosis	Up to 2413	BALP (Ostase); OC; urine CTx	Fracture (vertebral)	Relative risk of new vertebral fracture; multivariate analysis with OR indicating odds for suffering a new vertebral fracture for a 1 SD decrease in the variable
Garnero (1999)	RCT subgroup	Treatment monitoring – alendronate 2 years	Postmenopausal women with osteoporosis	307	BALP (Ostase) at baseline and 3, 6, 12 and 24 months.	BMD	Multivariate regression model; discriminative power (AUC ROC curve); accuracy

Abbreviations: AUC, area under the curve; BALP, bone alkaline phosphatase; BMD, bone mineral density; CTx, c-terminal telopeptide; MORE, Multiple Outcomes of Raloxifene Evaluation; OC, osteocalcin; OR, odds ratio; RCT, randomised controlled trial; ROC, receiver operator characteristic; SD, standard deviation.

Table 41 Study quality – monitoring treatment to prevent osteoporosis in peri/postmenopausal women without osteoporosis

Study	Selection bias minimised?	Follow-up sufficient?	Measurement bias minimised?	Confounding avoided?	Statistical analysis appropriate?	Comments
Bjarnason and Christiansen (2000)	Unclear. Includes all women who completed a RCT of HRT vs placebo (153/278). States that baseline characteristics of the population in this study were similar to those of the original RCT.	153/278 (%) completed the RCT. Only these women included in the present analysis. Therefore potential to bias the results.	Yes. BMD is the outcome and is measured independently from BALP.	Not reported.	Yes. Calculated sensitivity, specificity, NPV, PPV and area under the ROC curve. Cut-off for hip BMD was 0.14%. Cut-off for BALP was 20.6%.	
Dresner-Pollak (2000)	Unclear. Women recruited from a menopause clinic at a university hospital, but not stated how many approached or if this was a consecutive sample.	No. 63/90 (70%) completed the study. Only these women included in the analysis.	Yes. BMD is the outcome and is measured independently from BALP.	Not reported.	Yes. Calculated sensitivity, specificity, NPV, PPV and area under the ROC curve. Cut-offs for BMD were “maintained or gained bone” and “lost bone”. Cut-off for BALP was 40% decrease.	May be subject to selection bias owing to unclear recruitment, and analysis excludes 30% of women who did not complete study.
Delmas et al (2000b)	Unclear. Women included were part of two randomised trials of transdermal HRT, but not all were included in this study.	No. Only 374–388/569 (66%–68%) women included in analysis.	Yes. BMD is the outcome and is measured independently from BALP.	Not reported.	Unclear. Sensitivity, specificity, PPV and AUC ROC curve were calculated. Analyses separated into two groups: women who either did or did not respond (excluding those with a change in BMD within the known variability of BMD measurement) and all women. Cut-off values for BALP reported.	It is difficult to rule out selection bias owing to low percentage of women participating in study compared with total available population from 2 RCTs.
Marcus et al (1999)	Unclear. Only women from PEPI trial who were at least 80% compliant and had full data for 1 year were included.	No. 293/383 (77%) had >80% of medication and complete data up to 1 year. 72% had complete 3-year data.	Yes. BMD is the outcome and is measured independently from BALP.	Yes. Different potential confounders are included in the multiple regression models.	No. Placebo and active treatment groups were analysed separately. No adjustments made for multiple comparisons.	Possible selection bias due to proportion of women excluded from analysis and inappropriate statistical techniques used. Appears to be non-directed data analysis.

Abbreviations: AUC, area under the curve; BALP, bone alkaline phosphatase; BMD, bone mineral density; DEXA, dual X-ray absorptiometry; HRT, hormone replacement therapy; NPV, negative predictive value; PEPI, Postmenopausal Estrogen / Progestin Interventions Trial; PPV, positive predictive value; RCT, randomised controlled trial; ROC, receiver operator characteristic.

Table 42 Study quality – treatment monitoring in postmenopausal women with osteoporosis

Study	Selection bias minimised?	Follow-up sufficient?	Measurement bias minimised?	Confounding avoided?	Statistical analysis appropriate?	Comments
Bjarnason et al (2001)	Yes. RCT with serum samples for the evaluation of bone markers collected in a number of 'megasites' in Europe and in North and South America. 2622/7705 had serum samples collected, of which 2403 paired samples were available for BALP. Baseline characteristics of subgroup of women with serum samples match those of the entire randomised population.	Yes. 2403/2622 (92%) of potentially eligible women had paired samples for BALP.	Yes. BALP measured independently of fracture.	Yes. Adjustments were made for age, BMI, smoking status, BMD and prevalent vertebral fracture.	Yes. Two main analyses were performed: (i) the association between tertiles in BALP with the risk of vertebral fracture using a logistic regression model and (ii) a multivariate analysis of (i) including adjustment for confounders.	There is a low potential for bias is this study given the large patient numbers and the trial design and analysis. However, report results for the population level; may not necessarily be useful in helping to make individual clinical decisions.
Garnero (1999)	Yes. Women were part of an RCT of alendronate vs placebo (*n* = 994). Only women in the placebo and 10 mg/day dose of alendronate treatments were included (*n* = 307). Original placebo and 10 mg alendronate group totalled approximately 530.	No. Only approximately 53% of women eligible for inclusion in the study (ie, placebo or 10 mg alendronate) were included.	Yes. BALP measured independently of BMD.	Not reported.	Yes. Used level of BALP and % BALP as independent predictors of BMD in a multiple regression model.	There is a potential for selection bias in this study owing to the small number of potentially eligible women included in the study.

Abbreviations: BALP, bone alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; RCT, randomised controlled trial.

Monitoring of HRT in patients at risk of osteoporosis

Four studies used bone markers to determine response to HRT in postmenopausal women (Bjarnason & Christiansen 2000; Delmas et al 2000b; Dresner-Pollak 2000; Marcus et al 1999). The results of these studies should be viewed in relation to the recent controversies regarding combination HRT (see Tattersall 2002).

The aim of the study by Bjarnason and Christiansen (2000) (n = 153) was to investigate the utility of bone markers in predicting the prevention of bone loss by HRT. The women included in this study had completed a 3-year, single-centre, randomised controlled trial of HRT versus placebo (Bjarnason et al 2000); n = 278). The women were recruited by blinded, direct mail invitation based on social security numbers and were randomised either to one of four treatments of sequential or continuous oestradiol and gestodene treatment or to placebo. The results show that a change in BALP of ≥20.6 per cent after 6 months of treatment is reasonably accurate at predicting hip BMD after 3 years of therapy. As shown in Table 43, sensitivity was 85.5 per cent, specificity was 80 per cent, PPV was 92.2 per cent, and NPV was somewhat less at 66.7 per cent. The authors concluded that 'markers for bone resorption and formation have a high predictive value to estimate the outcome of HRT.' However, the resorption markers were superior to the formation markers (including BALP), and the authors stated that 'for follow-up on anti-resorptive interventions, resorption markers are preferable.'

The aim of the study by Dresner-Pollak et al (2000) (n = 90) was to examine the utility of BALP (Ostase) in predicting a response to HRT as measured by BMD in early menopausal women. Women were recruited from the Menopause Clinic of the Hadassah University Hospital and were randomly assigned to either continuous combination HRT (2 mg beta estradiol and 1 mg norethisterone for 28 days) or sequential combination HRT (2 mg beta estradiol for 12 days followed by 2 mg beta estradiol and 1 mg norethisterone for 10 days and 1 mg beta estradiol for the last 6 days). In addition, women who had undergone hysterectomy or oophorectomy within the previous month were placed on 2 mg estradiol daily. Women with the greatest decrease in BALP (≥50 per cent) at 6 months had the greatest increase in spine BMD at 2 years. A 40 per cent decrease in BALP at 6 months had moderate accuracy in predicting the highest quartile increase in lumbar spine BMD (Table 43). The area under the ROC curve for this analysis was 0.60. The authors concluded that a greater than 50 per cent decrease in BALP after 6 months of treatment 'suggests a positive skeletal response'. Seventeen per cent of women in this study did not have an increase in BMD after 2 years of treatment, so the authors suggested that measuring BALP after 6 months may play a role in identifying these non-responders early and help improve compliance.

Delmas et al (2000b) (n = 569) aimed to determine the utility of bone markers in monitoring response to HRT (matrix transdermal 17-beta-estradiol). The women included in this study were taken from two clinical trials with identical study design and were between 6 months and 6 years postmenopausal, with lumbar spine T-scores of 0 to 3. The results for responders and non-responders (ie, women with a change in BMD greater than or less than the known variation in BMD measurement: –2.26 to 2.26 per cent) showed very poor to moderate sensitivity (26.7%–63.6%) only when cut-offs were set so that specificity was at 90 per cent. Areas under the ROC curve ranged from 0.67 to 0.80 (see Table 43). The results for all patients, including those who showed no change in BMD, were even poorer, with sensitivity ranging from 17.3 to 44.3 per cent. The authors concluded that 'short-term change in bone markers reflects long-term changes of BMD'

in this patient group and suggested that these makers may have some utility in monitoring BMD response to HRT in individual postmenopausal women.

The aim of the study by Marcus et al (1999) (n = 293) was to measure the association of bone turnover markers with 1-year changes in BMD in postmenopausal women undergoing treatment with HRT (oestrogen alone or oestrogen and progestins) or placebo by regression analysis. The women in this study were a subgroup of the PEPI (Postmenopausal Estrogen / Progestin Interventions) trial, which was a 3-year, 7-site, randomised controlled trial in the USA comparing the effects of hormonal regimens on heart disease risk factors in healthy postmenopausal women. Three sites were involved in a secondary analysis examining the effects of the hormone regimens on BMD. For the active treatment group, 12-month change in BALP combined with baseline BMD, age and body mass index (BMI) was able to predict 14.5 per cent of the variance of 1-year change in spine BMD. In the treatment group the highest R^2 was seen for a combination of all baseline and change variables, but this still accounted for only 28.4 and 12.3 per cent of the variance for 1-year change in spine and hip BMD respectively. Therefore, none of the models examined in this study were able to accurately predict response to therapy. The authors concludes that the 'addition of bone marker data contributed very little to the prediction of BMD change in women treated with estrogen.'

These results relate to the ability of baseline and 12-month changes in BALP and other variables to predict 1-year BMD changes only. This is not consistent with the question being asked in this review (ie, can BALP measurement after a short duration of treatment predict longer-term responses to treatment?). However, the authors stated that the association between baseline and 12-month marker levels and 3-year BMD change was even smaller than that observed at 1 year.

Table 43 Summary of results – treatment monitoring in patients at risk of osteoporosis

Trial	Marker	Outcome	Sensitivity	Specificity	PPV	NPV	ROC curve	Regression analysis R^2 [a]	
	BALP	**BMD**	**%**	**%**	**%**	**%**	**AUC**	**Spine**	**Hip**
Bjarnason and Christiansen (2000)	**6 months**								
	Cut-off 1% change (20.6)	Total hip (?)	85.5	80.0	92.2	66.7	?		
	Cut-off 1 change from baseline (7.3 µg/L; 39%)	Total hip (?)	55.5	90.0	93.8	42.4	?		
	Cut-off 2% change (44.5)	Total hip (?)	36.4	97.5	97.6	35.8			
	Cut-off 2 change (5.4 µg/L; 54.7%)	Total hip (?)	29.1	97.5	97.0	33.3			
Dresner-Pollak (2000)	**6 months**	**Follow-up 2 years**							
	40% decrease	Lumbar spine	56	83	95	25	0.60		
Delmas et al (2000b)	**6 months**	**Follow-up 2 years**							
	Responders and non-responders only[b]								
	Cut-off (level 8.33 ng/mL)	Spine cut-off (>2.26% increase)	26.7	90[c]	87.4		0.67		
	Cut-off (percentage change –20.37%)	Spine cut-off (>2.26% increase)	49.4	90[c]	88.7		0.78		
	Cut-off (level and percentage change combined)	Spine cut-off (>2.26% increase)	63.6	90[c]	85.7		0.80		
	Responders, non-responders and no change								
	Cut-off (level 7.37 ng/mL)	Spine cut-off (>2.26% increase)	17.3	90[c]	81.1				
	Cut-off (percentage change –21.8%)	Spine cut-off (>2.26% increase)	41.9	90[c]	83.3				
	Cut-off (level and percentage change combined)	Spine cut-off (>2.26% increase)	44.3	90[c]	83.1				
Marcus et al (1999)		**Follow-up 3 years**							
	Baseline and/or 12 months	1-year percentage change						0.031–0.145	0.009–0.076
	Baseline and/or 12 months	3-year percentage change						< above	< above

Abbreviations: AUC, area under the curve; BALP, bone alkaline phosphatase; BMD, bone mineral density; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator characteristic.

[a] Coefficient of determination for multiple regression analysis. Assumes there is a dependency between the two variables being measured and can be interpreted as the percentage of the total variation in Y (eg, fracture or BMD) that is explained or accounted for by the variation or change in X (eg, BALP).

[b] Excludes patients who have no change in BMD (ie, between –2.26% and 2.26%).

[c] Specificity set at 90%.

Treatment monitoring in patients undergoing treatment for osteoporosis

Two studies examined the use of Ostase in monitoring treatment for osteoporosis (Bjarnason et al 2001; Garnero 1999). The study by Bjarnason et al (2001) used Ostase (and other marker tests) to monitor the treatment efficacy of raloxifene, using fracture as the outcome. Garnero (1999) used Ostase to monitor response to alendronate using BALP as a surrogate outcome. The results of these studies are summarised in Table 44 and Table 45.

The aim of the study by Bjarnason et al (2001) (n = 2312–2413) was to perform an exploratory analysis of the relationship between change in bone turnover (including BALP by Ostase) and fracture risk. Women available for inclusion in this study were the 2622 of the 7705 randomised to the Multiple Outcomes of Raloxifene Evaluation (MORE) study (Ettinger et al 1999) who had measurements of bone markers taken at baseline and after 6 and 12 months of treatment with raloxifene. Analysis of the baseline characteristics of the 2622 women potentially available for this study and the 7705 randomised to the MORE study showed that the two groups were very similar, but there are no further baseline data available for the smaller number of women (2403) with Ostase data. In the pooled raloxifene group (n = 1534), 87 women had fractures within the 3 years of the study. After adjustment for a number of factors, including age, smoking status, BMI, lumbar spine BMD and prevalent vertebral fracture status at baseline, a change in BALP (as measured by Ostase) at 6 months of –5.5 μg/L resulted in a 37 per cent decrease in the risk of fracture within 3 years ($P < 0.001$). After 12 months, a decrease in BALP of –5.91 μg/L resulted in a 25 per cent decrease in the risk of fracture ($P = 0.005$). Decreases in BALP in the placebo group at 6 and 12 months were shown to not be associated with a decrease in fracture risk ($P = 0.54$ for both). Therefore, these results suggest that a decrease in BALP can accurately predict a substantial decrease in fracture risk in osteoporotic women treated with raloxifene. However, these results are presented at the population, not individual, level.

The aim of the study by Garnero et al (1999) (n = 307) was to develop a model based on a combination of BALP marker level and percentage change (as measured by Ostase) at 6 months to predict long-term response in BMD. Women included in the study were a subgroup from a large randomised controlled trial of the effect of alendronate on BMD and fracture in postmenopausal osteoporotic women (Liberman et al 1995) (n = 994). Ostase had moderate sensitivity at predicting a change in vertebral BMD of at least 3 per cent, and the highest sensitivity (72%) when the level and the percentage change in Ostase were used together (assuming 90% specificity). The corresponding area under the ROC curve was 0.86. Regression analyses showed that Ostase was able to predict 34 per cent of the variance in vertebral BMD. Although the authors concluded that this model might be useful for the identification of non-responders, they note that, as a post-hoc analysis, 'prospective studies are thus recommended to estimate further the false-positive and false-negative rates obtained with this model.'

Table 44 Summary of results – utility of Ostase in monitoring treatment for osteoporosis in postmenopausal women, using fracture as an outcome

Trial	Marker	Outcome	RR (95% CI) *P* value	OR (95% CI) *P* value
	BALP	**Fracture**		
Bjarnason et al (2001)	**Raloxifene vs placebo**			
	6 months	**Follow-up 3 years**		
	Change (≤–5.7)	Vertebral fracture	0.38 (0.22, 0.68)	
	Change (–5.7 to ≤–1.19)	Vertebral fracture	0.74 (0.43, 1.25)	
	Change (>–1.9)	Vertebral fracture	1.05 (0.65, 1.25)	
				0.036[a]
	12 months			
	Change (≤–6.6)	Vertebral fracture	0.42 (0.23, 0.74)	
	Change (–6.6 to ≤–2.21)	Vertebral fracture	0.70 (0.41, 1.21)	
	Change (>–2.21)	Vertebral fracture	1.09 (0.68, 1.75)	
				0.045[a]
	Pooled raloxifene			
	6 months			
	Change (–5.5 µg/L)	Vertebral fracture		0.63 (0.50, 0.80) < 0.001
	Baseline prevalent fracture (1)	Vertebral fracture		3.26 (2.02, 5.27) < 0.001
	Spine BMD (0.13 g/cm^2)	Vertebral fracture		0.63 (0.50, 0.80) < 0.001
	12 months			
	Change (–5.9 µg/L)	Vertebral fracture		0.75 (0.62, 0.92) <0.005
	Baseline prevalent fracture (1)	Vertebral fracture		3.39 (2.08, 5.54) < 0.001
	Spine BMD (0.13 g/cm^2)	Vertebral fracture		0.64 (0.50, 0.83) < 0.001

Abbreviations: BALP, bone alkaline phosphatase; BMD, bone mineral density; CI, confidence interval; OR, odds ratio; RR, relative risk.

[a] Indicate the presence of a differential anti-fracture efficacy across tertiles for a model including tertile, therapy and tertile × therapy.

Table 45 Summary of results – utility of Ostase in monitoring treatment for osteoporosis in postmenopausal women, using BMD as a surrogate outcome for fracture

Trial	Marker BALP[a]	Outcome BMD	Sensitivity (%)	PPV	NPV	Regression[b] coefficient (± SEM)	Standardised[c] regression coefficient (± SEM)	Partial correlation coefficient[b] *P* value	Multiple regression coefficient (r^2)	ROC curve AUC
Garnero (1999)	**6 months**	**Follow-up 2 years**								
	Level (≤9.5 µg/L)	≥3% change vertebral BMD	59[c]	84	73					
	Percentage change (≤–38.2)	≥3% change vertebral BMD	61	83	74					
	Level + percentage change	≥3% change vertebral BMD	72	85	80					
	Level (≤9.4 µg/L)	Alendronate vs placebo	66	85	78					
	Percentage change (≤–38.5)	Alendronate vs placebo	71	85	80					
	Level + percentage change	Alendronate vs placebo	82	87	87					
	Level	Vertebral BMD				–0.28 ± 0.06	–0.29 ± 0.06	–0.25 (<0.001)		
	Percentage change	Vertebral BMD				–0.07 ± 0.01	–0.34 ± 0.06	–0.34 (<0.001)		
	Level + percentage change	Vertebral BMD							34%	
	Level	≥3% change vertebral BMD								0.82[d]
	Percentage change	≥3% change vertebral BMD								0.83[d]
	Level + percentage change	≥3% change vertebral BMD								0.86[d]
	Level	Alendronate vs placebo								0.89[d]
	Percentage change	Alendronate vs placebo								0.91[d]
	Level + percentage change	Alendronate vs placebo								0.93[d]

Abbreviations: AUC, area under the curve; BALP, bone alkaline phosphatase; BMD, bone mineral density; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator characteristic.

[a] Controlled for other independent variable added in the model (ie, level or percentage change).

[b] Regression coefficients that would have been obtained if all independent variables had been standardised to a mean of 0 and SD = 1.

[c] Assuming 90% specificity.

[d] Estimated from graphs.

Impact of Ostase on clinical management

In some studies Ostase appears to be moderately accurate in predicting fracture risk and treatment response and thus could be used to alter patient management by instituting treatment earlier or by changing therapy if the original is not working. However, no studies were identified which examined the impact of Ostase on clinical management. Therefore, the utility of Ostase in this role could not be determined.

Impact of Ostase on patient outcomes

Early treatment for the prevention of osteoporosis and altering non-effective therapy could improve outcomes for patients by reducing fracture risk or improving a patient's quality of life. For example, in the decision-analytic model by (Chapurlat & Cummings 2002), the authors found that measuring treatment response early by using a bone resorption marker had a small effect on quality of life. However, no studies were identified which examined the specific impact of Ostase on patient outcomes or more generally looked at the effect on outcomes of early changes of therapy for non-responders. Therefore, the utility of Ostase in this role could not be determined.

Existing Health Technology Assessment reports

Two reports addressing the use of biochemical markers in osteoporosis were identified (Nelson et al 2001; Smith & Greer 2001). Although both reviews assessed the use of biochemical markers in general, they included studies examining the use of Ostase in osteoporosis. Details of the methodology of these reviews can be found in Table 52 in Appendix C.

The report by the Agency for Healthcare Research and Quality (AHRQ) (Nelson et al 2001) was a very thorough and high-quality systematic review. The results of the AHRQ review that relate specifically to this review of Ostase are summarised as follows:

- Do markers predict fracture?

  Three prospective studies and three nested case-control studies were examined. The results of the EPIDOS study showed that BALP was not a significant predictor of fracture. The report concluded that no marker was associated with increased fracture risk, and that although the EPIDOS study suggests that using markers with BMD increases predictability, no other studies have confirmed this.

- Can markers help select patients for treatment?

  Eleven longitudinal studies show the association between mean group marker levels and rates of bone loss measured by BMD at follow-up. In the SOF, BALP was not significantly correlated with DEXA. One of three studies examining BALP found a significant correlation with bone loss. The report concluded that there was no clear trend between markers and bone loss, and that sensitivity and specificity were too low to be useful in selecting patients for treatment. Some studies showed improved accuracy when two or more markers were used in combination.

- Can markers predict response to therapy?

  Six longitudinal studies examining the prediction of response to alendronate were evaluated. Four studies compared BALP to spine DEXA at 12–30 months, and the correlation coefficients ranged from –0.06 to –0.67; 3 were statistically significant. Hip DEXA (2 studies) and total body and wrist DEXA were not significantly associated with BALP.

  Eleven studies prospectively studied prediction of response to HRT. One study showed that BALP at 6 months had 56 per cent sensitivity, 83 per cent specificity, 95 per cent PPV and 25 per cent NPV at predicting gain in BMD at 2 years. There was no association between hip DEXA and percentage change in BALP. In another study, BALP at 3 and 6 months was correlated with DEXA at 2 years. BALP was inaccurate at 3 months but slightly improved at 6 months. In another study where cut-offs were set to keep false-positive rates low, sensitivity was low for BALP. The report concludes that there is a small correlation between markers and DEXA but they are not reliable enough to predict response in individual patients. The best results in the EPIDOS study have not been replicated.

The report by the Institute for Clinical Systems Improvement (ICSI) (Smith & Greer 2001) was poorly reported, giving little methodological information, making it hard to assess the validity of the review. However, the report includes an assessment of the studies included in the current review.

The main conclusions of the ICSI report which relate to the questions addressed in this review were as follows:

- An individual's fracture risk cannot be predicted from bone marker measurements, despite some population-based evidence that increases in biochemical bone markers are associated with increased fracture risk. Only one of the seven studies evaluated provided data on diagnostic accuracy (ie, sensitivity and specificity) that would allow one to determine the utility of markers in predicting risk in individual patients.

- The use of bone markers to monitor bone loss and to identify potential fast and slow bone losers is of limited value. Some studies suggested that it is of little value, but others showed statistically significant but low ($r \leq 0.4$) correlations between markers and initial BMD or change in BMD.

- Despite evidence that some markers are responsive to certain treatments, there was no clear evidence that bone markers can be used to predict future BMD response in individual patients or that they can be used to help select therapies for patients. Studies examining the use of markers to monitor HRT have shown variable results: some suggest that markers can predict longer-term changes in BMD, while others show no such association. Studies examining the monitoring of other therapies (including alendronate) have shown statistically significant, moderate correlations between changes in markers at 3 to 6 months compared with 2-year changes in BMD. The authors concluded that the evidence regarding the use of bone markers in monitoring therapy is inconsistent between studies and not strong, because no more than 23 per cent of the variability in 1- to 3-year changes in BMD was accounted for by changes in bone formation markers.

- There was no evidence to support the claim that bone markers could be used to improve patient compliance with therapy.

In summary the findings of the AHRQ and ICSI reviews are consistent with the findings of this current review. A number of studies have been published since these reviews, but the results of these do not significantly change the conclusions of the above reviews.

Conclusions

- The conclusions regarding the diagnostic accuracy of BALP as measured by Ostase in the prediction of fracture risk and monitoring of treatment are based on a number of studies.
- The extent to which conclusions can be drawn from the available evidence is limited by the presence of methodological biases in most of the studies.
- With regards to the potential role of Ostase in predicting future fracture risk, the evidence is poor, and many studies present conflicting results. A number of these studies suggest that BALP as measured by Ostase is not a good predictor of future fracture. In addition, some studies suggest that bone resorption markers may be of greater usefulness.
- With regards to the potential role of Ostase in monitoring treatment with HRT, the results are variable. Some studies suggest that Ostase (or bone markers in general) may be of use in monitoring HRT, although the resorption markers may be superior.
- With regards to the potential role of Ostase in monitoring treatment for osteoporosis, the results of the large, high-quality study by Bjarnason et al (2001) suggest that a decrease in BALP as measured by Ostase can predict a substantial proportion of the decrease in fracture risk in osteoporotic women treated with raloxifene. However, no data regarding diagnostic accuracy are reported, so caution is required when applying the results of this population study at the individual level.
- There is insufficient evidence to indicate the role of Ostase in improving health outcomes and altering management in patients with osteoporosis.
- Furthermore, there is currently no evidence available that shows that changing treatment in non-responders after 6 months (as tested by Ostase) rather than 12–24 months (as tested by BMD) has any impact on long-term outcomes. Therefore, further research in the areas of changes in patient management and patient outcomes is still required.
- It has been suggested that patient adherence and compliance may be improved by feeding back information on decreases in BALP following treatment. However, there is currently insufficient evidence available for this use.

What are the economic considerations?

The price suggested by the applicant ($24.35) for Ostase would be equivalent to the Schedule Fee for existing biochemical bone marker tests that measure the products of collagen breakdown, listed on the MBS (items 66773 and 66776).

However, as the effectiveness of Ostase has yet to be conclusively determined, it is not possible to perform an economic analysis of its role in any of the indications assessed.

Although a number of studies reported that Ostase may accurately measure BALP, there is currently insufficient evidence to suggest that Ostase provides any benefit to patients as a replacement or incremental test in Paget's disease of bone, renal osteodystrophy, prostate cancer or osteoporosis.

Conclusions

Performance characteristics

- In the determination of serum BALP levels, a reasonably strong correlation was reported among the Ostase tests and between the Ostase tests and electrophoresis.
- A cross-reactivity of about 10 per cent occurs with alkaline phosphatase of liver origin. This may limit the utility of this test in patients with significant elevations of LALP.
- Within- and between-run precision appear satisfactory for clinical use.
- The limit of detection of the assay allows measurement of BALP down to levels below those found in healthy persons.
- No information on the sensitivity or specificity of the Ostase tests compared with each other or with electrophoresis was reported.

Safety

Ostase is an *in vitro* diagnostic laboratory test that measures BALP in human sera. As such, there is no safety risk to patients. Laboratory staff and organisations intending to use the Ostase laboratory kit should ensure the safe handling of blood and other fluids as outlined in the health and safety guidelines of the National Pathology Accreditation Advisory Council.

Effectiveness

Diagnostic accuracy

The conclusions regarding the diagnostic accuracy of BALP for Paget's disease of bone, renal osteodystrophy, prostate cancer and osteoporosis are based on a small number of studies. Many of the studies also show methodological biases, which further limit the extent to which inferences can be applied to the wider clinical population. On the basis of the evidence available, it would appear that Ostase has the potential to be useful as a supplementary test in the diagnosis of Paget's disease of bone, differentiation of renal osteodystrophy, diagnosis of bone metastases in prostate cancer, and monitoring treatment in women with osteoporosis. However, supportive evidence of the diagnostic accuracy of Ostase is required from larger, more representative studies.

Impact on clinical decision-making and health outcomes

As no studies were retrieved that specifically assessed the role of Ostase in clinical decision-making or its effect on patient outcomes, it was not possible to assess its impact in these areas. Therefore, the clinical value of the determination of BALP by Ostase was not adequately demonstrated in the studies reviewed to date.

Indication-specific findings

Paget's disease of bone

The specific research questions in relation to this review were:

- What is the additional value of Ostase to TALP in the diagnosis of Paget's disease of bone in patients suspected to have the condition?
- What is the value of Ostase compared with TALP in the monitoring of patients who have undergone pharmacological treatment for Paget's disease of bone?

MSAC's conclusions

- The conclusions regarding the diagnostic accuracy of BALP in the diagnosis of Paget's disease of bone are based on a very small amount of evidence.
- Although some studies suggest that Ostase is a more sensitive marker of bone turnover than TALP, and therefore may play a role in assisting in the diagnosis of Paget's disease of bone, there is currently insufficient evidence at this time to draw any definitive conclusions.
- There is limited evidence at this time to indicate the role of Ostase in the monitoring of treatment responses in patients with Paget's disease of bone.
- There is currently insufficient evidence to indicate the role of Ostase in improving health outcomes and altering management in patients with Paget's disease of bone.

Renal osteodystrophy

- What is the additional value of Ostase to other biochemical measures in the diagnosis and differentiation of the different patterns of bone disease in patients with prolonged low renal function (GFR < 30 mL/min)?
- What is the additional value of Ostase to other biochemical measures in the monitoring of treatment in patients with renal osteodystrophy?

MSAC's conclusions

- The conclusions regarding the diagnostic accuracy of BALP in the differential diagnosis of renal osteodystrophy are based on a relatively small body of evidence.
- A number of methodological limitations exist in the studies reporting on BALP and renal osteodystrophy.

- On the basis of the evidence presented it would appear that Ostase has the potential to play a role in the differential diagnosis of renal osteodystrophy. In the populations reported on it would seem that the diagnostic accuracy of BALP alone or in combination with iPTH is better than that of TALP alone or TALP and iPTH combined. However, it is difficult to generalise the results given the small number of patients with adynamic bone disease reported on in the studies.

- Further evidence is needed in terms of the role of Ostase in the monitoring of treatment response.

- There is insufficient evidence at this time to indicate the role of Ostase in improving health outcomes and altering management in patients with impaired renal function.

Prostate cancer

- What is the additional value of Ostase to PSA and TALP in determining the extent of bone metastases as detected on bone scans (i) in the initial staging of disease, and (ii) during follow-up after treatment in patients with prostate cancer?

- What is the additional value of Ostase to PSA and TALP in the monitoring of therapy in patients with prostate cancer and bone metastases?

MSAC's conclusions

- The conclusions regarding the diagnostic accuracy of BALP as measured by Ostase in the diagnosis and treatment monitoring of prostate cancer bone metastases are based on a very small amount of evidence.

- In the populations reported on in the above studies, BALP as measured by Ostase in combination with PSA appears to have a higher sensitivity and specificity than BALP or PSA alone in the detection of bone metastases at initial staging and during follow-up. However, the extent to which conclusions can be drawn from the available evidence is limited by the presence of methodological biases in many of the studies.

- There is limited evidence at this time to indicate the role of Ostase in the monitoring of treatment responses in patients with bone metastases of prostate cancer.

- There is currently insufficient evidence to indicate the role of Ostase in improving health outcomes and altering management in patients with bone metastases of prostate cancer.

- At this stage there is insufficient evidence to suggest that the institution of early treatment in asymptomatic patients with prostate cancer diagnosed with bone metastases confers any overall benefit. Further research is still required to more definitively evaluate the efficacy and adverse effects of early versus late therapy.

Osteoporosis

- What is the additional value of Ostase to measurement of BMD by DEXA in determining the risk of fracture in patients at risk of osteoporosis?

- What is the additional value of Ostase to measurement of BMD by DEXA in the monitoring of therapy in patients being treated to prevent or minimise osteoporosis?

MSAC's conclusions

- The conclusions regarding the diagnostic accuracy of BALP as measured by Ostase in the prediction of fracture risk and monitoring of treatment are based on a small number of studies.

- The extent to which conclusions can be drawn from the available evidence is limited by the presence of methodological biases in most of the studies.

- With regards to the potential role of Ostase in predicting future fracture risk, the evidence is poor, and many studies present conflicting results. A number of these studies suggest that BALP as measured by Ostase is not a good predictor of future fracture. In addition, some studies suggest that the bone resorption markers may be of greater use.

- With regards to the potential role of Ostase in monitoring treatment with HRT, the results are variable. Some studies suggest that Ostase (or bone markers in general) may be of use in monitoring HRT, although resorption markers may be superior.

- With regards to the potential role of Ostase in monitoring treatment for osteoporosis, the results of the large, high-quality study by Bjarnason et al (2001) suggest that a decrease in BALP as measured by Ostase can predict a substantial proportion of the decrease in fracture risk in osteoporotic women treated with raloxifene. However, no data regarding diagnostic accuracy is reported, so caution is required when applying the results of this population study at the individual level.

- There is insufficient evidence to indicate the role of Ostase in improving health outcomes and altering management in patients with osteoporosis.

- Furthermore, there is currently no evidence that shows that changing treatment in non-responders after 6 months (as tested by Ostase) rather than 12–24 months (as tested by BMD) has any impact on long-term outcomes. Therefore, further research in the areas of changes in patient management and patient outcomes is still required.

- It has been suggested that patient adherence and compliance may be improved by feeding back information on decreases in BALP following treatment. However, there is currently insufficient evidence available for this use.

Cost-effectiveness

The price suggested by the applicant ($24.35) for Ostase would be equivalent to the Schedule Fee for existing biochemical bone marker tests that measure the products of collagen breakdown, listed on the MBS (items 66773 and 66776).

However, as the effectiveness of Ostase has yet to be conclusively determined, it is not possible to perform an economic analysis of its role in any of the indications assessed. Although a small number of studies reported that Ostase may accurately measure BALP, there is currently insufficient evidence to suggest that Ostase provides any benefit to

patients as a replacement or incremental test in Paget's disease of bone, renal osteodystrophy, prostate cancer or osteoporosis.

Recommendation

Since there is currently insufficient evidence pertaining to the effectiveness and cost-effectiveness of Ostase diagnostic laboratory tests (Tandem-R Ostase, Tandem-MP Ostase and Access Ostase) in the diagnosis and monitoring of treatment in Paget's disease of bone, renal osteodystrophy, bone metastases of prostate cancer and osteoporosis, MSAC recommended that public funding should not be supported at this time for these tests.

The Australian Government Minister for Health and Ageing accepted this recommendation on 8 August 2003.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;

- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;

- advise the Minister for Health and Ageing on references related to new or existing medical technologies and procedures; and

- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council and report its findings to the council.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Ian Fraser	reproductive medicine
Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Dr Ewa Piejko	general practice
Mr Chris Sheedy	Assistant Secretary, Diagnostics and Technology Branch, Department of Health and Ageing
Professor John Simes	clinical epidemiology and clinical trials

Professor Richard Smallwood	Chief Medical Officer, Department of Health and Ageing
Dr Robert Stable	representing the Australian Health Ministers' Advisory Council
Professor Bryant Stokes	neurological surgery
Associate Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Supporting committee

Supporting committee for MSAC application 1044 Ostase

Professor Syd Bell (Chair) MBBS, FFPH, MRACP, FRCPA, MD Area Director of Microbiology South East Sydney Area Health Service	member of MSAC
Associate Professor Peter Ebeling MBBS, FRACP, MD Endocrinologist Department of Diabetes and Endocrinology Royal Melbourne Hospital and Department of Medicine The University of Melbourne	nominated by the Endocrine Society of Australia
Professor Jane Hall PhD Director, Centre for Health Economics Research and Evaluation The University of Technology, Sydney	member of MSAC
Dr Helen Healy MBBS, FRACP, PhD Director Department of Renal Medicine Royal Brisbane Hospital	nominated by the Australian and New Zealand Society of Nephrology
Clinical Associate Professor Michael J Hooper MBBS, FRACP University of Sydney Area Head, Bone and Mineral Stream Endocrinology Central Sydney Area Health Service	nominated by the Royal Australasian College of Physicians
Ms Rebecca James Consumer health advocate	member of MSAC
Dr Graham Jones BSc (Med), DPhil, MBBS, MAACB, FAACB, FRCPA Staff Specialist Department of Chemical Pathology St Vincent's Hospital, Sydney	nominated by the Australian Association of Clinical Biochemists
Dr David Malouf MBBS, FRACS (Urology) Consultant Urologist, Sydney	nominated by the Urological Society of Australasia

Dr Jitendra Parikh
MBBS, MD, DGO, MRACGP, ACCAM,
Dip Em Med, MPM, MFM
General Practitioner, Sydney

nominated by the Royal Australian College of General Practitioners

Dr Samuel Vasikaran
MBBS, MSc, MD, FRCPA
Head, Department of Core Clinical Pathology & Biochemistry
Consultant, Osteoporosis Clinic
Royal Perth Hospital

nominated by the Royal College of Pathologists of Australasia

Please note that all abbreviations are described in Appendix H.

Table 46 Detection of Paget's disease with Ostase

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standards	Outcomes
Alvarez et al (1995)								
59	Not stated	To investigate the diagnostic accuracy of a range of biochemical markers in Paget's disease of bone	Pts with Paget's disease confirmed with X-ray and bone scan 64 ± 10 (39–84) y Liver and kidney function tests normal No previous treatment for 6 months Classified into three groups: I: (*n* = 15) TALP < 250 U/L II: (*n* = 18) TALP 251–500 U/L III: (*n* = 26) TALP > 500 U/L	Cross-sectional Case-series Unclear if consecutive series Level IV	BALP (Tandem-R Ostase) Not all tests were not performed in some patients Unclear if tests assessed independent of other clinical information or tests	TALP PTH Ca PO_4 $Ca_3(PO_4)_2$	Difficult to determine from paper – could be X-ray and bone scans	Compared distributions between tests. Determined correlation between tests. Diagnostic accuracy assessed with ROC curves. Results are difficult to interpret: BALP: When Sp = 100%, Sn = 84% TALP: When Sp = 100%, Sn = 78% Differences in sensitivity between tests occurred because nine patients with normal TALP had increased BALP.
Comments: Paper difficult to interpret; unable to check calculations for the diagnostic measures provided by the authors.								

No of pts	Time period	Study aim	Population	Study type, level	New Test	Comparator	Reference standards	Outcomes
Woitge (1996)								
355	Not stated	To investigate the usefulness of BALP compared with TALP in the diagnosis of conditions affecting bone metabolism	Consecutive series (*n* = 355), stratified into three groups: (i) healthy adults (*n* = 199) (ii) hospitalised patients with non-skeletal disease (*n* = 123) (iii) hospitalised patients with metabolic bone disease (*n* = 113) *n* = 26 of group (iii) had Paget's disease of bone	Cross-sectional Consecutive case-series Level IV	BALP (Tandem-R Ostase) Unclear if results were reviewed independent of the other clinical findings and reference standard	TALP	Upper limit of normal (ie, mean of the healthy control group + 2 SD).	ROC curve analysis indicated that the areas under the curve for TALP and BALP were 0.945 and 0.979, respectively. Reference ranges were obtained from the healthy adult group. Positive test was defined as above the upper limit of the normal reference range. Diagnostic accuracy was calculated for postmenopausal women and male Paget's disease subgroups. Results: Test BALP TALP Premenopausal women >20.2 ng/mL 171.2 U/L Sn 83% 83% Males: 18 ng/mL 181.5 U/L Sn 100% 100%
Comments: Unable to determine any other diagnostic values from paper. Unable to check calculations for sensitivity.								

Table 47 Diagnosis and differentiation of renal osteodystrophy by Ostase

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standard	Outcomes
Coen et al (1998)								
41	Not stated	Compare PTH with a range of markers – looking at measures of bone turnover	18 females 23 males Chronic renal failure treated with haemodialysis Recruited from several units in Rome	Case-series Level IV	BALP (Tandem-Ostase) Normal values 11.8 ± 4.3 ng/mL	iPTH TALP OC TRAP PICP Dpy Ca PO_4 25-hydroxychole-calcified	Bone biopsy (all patients) 37/41 patients had biopsy after double tetracycline administration	Divided pts into three groups: ABD, MO, HPT Correlation information When only PTH and BALP were used a correct classification of MO + HPT and LTBD was possible in 90.6% and 88.9% respectively. Predictive value of MO + HPT was 96.7% and for LTBD was 72.7%. PTH and ALP were used. A correct classification of MO + HPT and LTBD was possible in 81.3% and 88.9% respectively. Predictive value of MO + HPT was 96.3% and for LTBD was 57.2%.
Comments: Patients had received calcium salts as chelating agents; 16 patients received aluminium hydroxide in addition to phosphate chelating calcium salts. A number of bone variables were measured, including bone volume, osteoid volume. Type of renal osteodystrophy – morphological criteria. No patients with osteomalacia. Population had limited aluminium exposure. PTH cut-off levels were also less than in other reports.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standard	Outcomes
Couttenye et al (1996)								
103	Not stated	To assess the value of different biochemical serum markers in the diagnosis of ABD	Chronic haemodialysis patients from different countries 53 female 50 male	Case-series Level IV	BALP by electrophoresis	TALP iPTH OC	Bone biopsy – double tetracycline labelling	Results BALP ≤ 27 U/L Sn 78.1% Sp 86.4% PPV 75% NPV 88% iPTH ≤ 150 pg/mL Sn 80.6% Sp 76.2% PPV 65% NPV 88% TALP ≤ 123 U/L Sn 75% Sp 83.1% iPTH + BALP Sn 67.7% Sp 91.5% OC results were also reported, but not stated here
Comments: 89 patients had phosphate binders; 42 received vitamin D therapy; 4 did not receive phosphate binders. Classification of osteodystrophy based on criteria described by Salusky et al Patients with severe liver disease were excluded from the study – therefore should be cautious about the fact that TALP and iPTH + BALP had similar results. Not all patients had all tests.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standard	Outcomes
Fletcher et al (1997)								
73	Not stated	To determine the relative efficacy of non-invasive techniques to diagnose renal osteodystrophy	39 males 34 females Dialysis units from two hospitals Median time on dialysis 3 years	Cross-sectional case series Level IV	BALP (Tandem-R Ostase) For patients on haemodialysis samples were taken before dialysis	iPTH TALP Al Ca_2 BMD Ultrasound Radiographic analysis	73 patients had bone biopsy. 20 had received tetracycline double labelling. However, only 57 were able to be read; the remaining 16 were damaged.	Correlation information iPTH / BALP / ALP with histomorphometric information Results Diagnosis of HPT a serum iPTH > 100 pg/mL had Sp 66% and Sn 81%. Diagnosis of HPT serum BALP > 10 ng/mL had Sp 92% and Sn 70%. Diagnosis of HPT ALP > 300 IU/L had Sp 100% and Sn 30%. Diagnosis of HPT serum iPTH > 100 pg/mL, BALP > 10 ng/mL had Sp 100% and Sn 66%. Diagnosis of HPT a serum iPTH, ALP had Sp 100% and Sn 30%.
Comments: Table 1 in paper outlines distribution of renal disease in the study population. In the absence of aluminium staining a diagnosis of ABD was made by two independent observers. In patients with normal histology, author reports LTBD, mild HPT, no significant difference in iPTH, BALP or ALP. Markers were unable to differentiate the bone pathologies in these patients. Normal reference range for BALP is quoted as < 19 ng/mL. Note that there is a high incidence of hyperparathyroidism in the study, owing to patient selection.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standard	Outcomes
Jarava et al (1996)								
56	Not stated	To determine correlation information between BALP and other markers To look at relationship between BALP and histomorpho-metric parameters	32 males 34 females Chronic renal failure treated with haemodialysis Treatment 71 ± 53 months	Case series Level IV	BALP: (Tandem-R Ostase Normal range 8–16 ng/mL Intra and inter-assay coefficients	iPTH TALP OC	Bone biopsy 20/56 patients OF in 15 patients Mild OF 2 patients MO I patient ABD 1 patient Normal 1 patient	Correlation information (iPTH / TALP / BALP / OC) BALP correlation significant with other humoral parameters with a correlation coefficient of 0.79 with PTH and 0.84 with TALP.
Comments: Treatment: aluminium hydroxide, calcium carbonate. None of the patients had evidence of liver disease. A number of histological parameters were measured. Note that although correlations are high they do not indicate diagnostic accuracy.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standard	Outcomes
Urena et al (1996)								
42	Not stated	To determine the diagnostic value of plasma BALP in the non-invasive evaluation of bone turnover	19 women, 23 men maintenance haemodialysis mean duration of treatment 7.7 y	Case-series Level IV	BALP (Tandem-R Ostase) HTBD – BALP > 20 ng/mL LTBD – BALP < 20 ng/mL	iPTH > 200 pg/mL AI Ca_2 TALP > 200 IU/L	Bone biopsy (42 patients) 17 patients bone biopsy after tetracycline double labelling Bone scan was read in duplicate by two persons blinded to biochemistry results.	Correlation information Plasma BALP levels were positively correlated with iPTH (r = 0.82). Subgroups with some discrepancies were observed. Sensitivity and specificity reported for HTBD and LTBD for iPTH, TALP, BALP and iPTH + BALP. A range of cut off points were used as outlined in Table 3 in paper: iPTH (pg/mL) 150, 200; TALP (IU/L) 150, 175, 200; BALP (ng/mL): 10, 15, 20; iPTH 200 pg/mL; BALP 20 ng/mL. As the paper primarily reports for iPTH 200, TALP 200 and BALP 20, this is what is reported below. HTBD / iPTH: Sn = 72%; Sp = 80%; PPV = 92%; NPV = 47% LTBD / iPTH: Sn = 80%; Sp = 72%; PPV = 47%; NPV = 92% HTBD / TALP: Sn = 50%; Sp = 90%; PPV = 94%; NPV = 36% LTBD / TALP: Sn = 90%; Sp = 50%; PPV = 36%; NPV = 94% HTBD / BALP: Sn = 100%; Sp = 100%; PPV = 84%; NPV = 100% LTBD / BALP: Sn = 100%; Sp = 100%; PPV = 100%; NPV = 84% HTBD / iPTH + BALP: Sn = 100%; Sp = 80%; PPV = 94%; NPV = 100% LTBD / iPTH + BALP: Sn = 80%; Sp = 100%; PPV = 100%; NPV = 94%
Comments: Patients had received calcitriol or phosphate binding therapy. Patients were separated into two groups: HTBD and LTBD. ABD was also considered. Only one patient had ABD.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standard	Outcomes
Woitge (1996)								
355	Not stated	To compare TALP with three measures of BALP	119 healthy adults 123 patients with non-skeletal disease 113 with metabolic bone disease 47 patients with chronic renal failure 35 patients with secondary hyperparathyroidism (SHPT)	Cross-sectional Consecutive case series Level IV	BALP (Tandem R-Ostase)	TALP L-BALP (lectin precipitation method) BALP (Alkphase B)	Upper limit of normal (ie, mean for the health control group + 2 SD)	Area under the curve reported for SHPT TALP 0.689 (range, 0.517–0.709) BALP 0.601 (range, 0.499–0.703)
Comments: Unable to determine any other diagnostic values from paper. Unable to check calculations for sensitivity.								

Table 48 Additional value of Ostase in the detection of bone metastases in the initial staging of prostate cancer

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standards	Outcomes
Morote et al (1996)								
140	1992–1995	To investigate the clinical utility of PSA and BALP in a prostate carcinoma population with a high prevalence of bone metastases	Newly diagnosed and histologically proven patients with prostate cancer M0 (*n* = 72) & M1–4 (*n* = 68) Mean age 71.2 ± 8.3 y (44–86 y) Patients excluded if precise clinical status could not be determined	Prospective Cross-sectional Not clear from paper whether consecutive series Level IV	BALP (Tandem-R Ostase) Both tests were performed in all patients. Not clear from paper if tests were assessed independent of other clinical results. Assume measured independent of reference standard because prospective design – but not clear from paper.	PSA	Bone scan (CT, MRI or bone marrow scintigraphy also used to clarify hot spots) Not clear from paper if tests were assessed independently. All patients had reference standard. Unclear if results were influenced by verification bias.	Mann-Whitney *U* to compare mean values of BALP and PSA across M0–M4 disease ROC curves: BALP 25 ng/mL; Sn 98.1%; Sp 85.3%; BALP better than PSA Diagnostic accuracy results Tests BALP 20 ng/mL BALP 30 ng/mL Sn 92.6% 79.4% Sp 87.5% 98.6% PPV 87.5% 98.2% NPV 92.6% 83.5% Acc 90% 89.3% Tests PSA 10 ng/mL PSA 20 ng/mL Sn 98.5% 97.1% Sp 9.7% 30.6% PPV 50.8% 56.9%^ NPV 87.5% 91.7% Acc 52.9% 62.9% Tests BALP 20 ng/.mL PSA 20 ng/mL BALP 30 ng/mL PSA 20 ng/mL Sn 100% 98.5% Sp 94.4% 98.6% PPV 94.4% 98.5% NPV 100% 98.6% Acc 97.1% 98.6%

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standards	Outcomes
Lorente et al (1999)								
295	Nov 1992 – Dec 1996	To investigate the clinical utility of BALP in addition to PSA in the staging of newly diagnosed, untreated patients with prostate cancer	Newly diagnosed, untreated patients with histologically proven prostate cancer Mean age 72 y (42–96) Patients for which a precise clinical assessment could not be determined were excluded. *n* = 202 M0 *n* = 93 M1	Cross-sectional Prospective Consecutive series Level IV	Tandem®-R Ostase Tests were conducted in all patients Unclear whether tests assessed independently.	PSA	Bone scans (some had CT, MRI or bone marrow scintigraphy for clarification) Unclear whether assessed independent of other results. All patients had reference standard. No verification bias.	Multiple regression used to determine the influence of several clinical parameters on both serum marker levels. Compared mean values (Mann Whitney *U*) of BALP and PSA across M1–M4 disease Area under the ROC curve: BALP + PSA = 0.9551 (SE = 0.0159) Diagnostic accuracy results: Test / PSA 8 ng/mL / PSA 10 ng/mL Sn 100% 98.9% Sp 17.8% 24.2% PPV 35.9% 37.5% NPV 100% 98% PPV 35.9% 37.5% Acc 43.7% 47.8% Test / PSA 20 ng/mL / BALP 20 ng/mL Sn 96.7% 86% Sp 48% 92.5% PPV 46.1% 84.2% NPV 97% 93.5% Acc 63.4% 90.5% Test / BALP 20 / PSA 20 ng/mL Sn 100% Sp 47% PPV 46.5% NPV 100% Acc 63.7%
Comments: Possibly includes same patient group as Morote et al (1996). Adds some comments on the potential cost-effectiveness of BALP in addition to PSA.								

Table 49 Additional value of Ostase in the detection of bone metastases in patients with prostate cancer (untreated and treated)

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standards	Outcomes
Lorente et al (1996)								
350 (long-term study *n* = 61)	Not stated	To investigate the usefulness of BALP and PSA in determining bone metastases as determined on bone scan in patients with prostate cancer	Newly diagnosed, treated and untreated patients Men with metabolic bone disease excluded *n* = 350: 150 controls (50–70 y) 100 BPH (45–85 y) 100 prostate cancer (44–90 y) M0 (T1–4) *n* = 52 M1 (T1–4) *n* = 48 Longitudinal study: 64.2 months (3–217) *n* = 61 T1–4N0-XM0	Cross-sectional Case-series Not clear from paper whether consecutive series Level IV	BALP (Tandem®-R Ostase) Both tests conducted in all patients. Not clear from paper whether test measured independently of the PSA test or clinical results.	PSA	Bone scan All patients had reference standard. Not clear from paper whether reference standard measured independently of other tests.	Comparison of mean BALP and PSA values across groups. Diagnostic accuracy to determine presence of bone metastases. Cut-off values set at 30 ng/mL BALP, 100 ng/mL PSA. Test / BALP / PSA / BALP and/or PSA Sn 87.5% 79.1% 95.8% Sp 100% 84.6% 100% PPV 100% 82.6% 100% NPV 89.6% 81.5% 95.6% Acc 93.7% 81.8% 97.9% The values reported are for patients with positive BALP **and / or** PSA. Diagnostic accuracy results also reported on for BALP > 30 ng/mL and PSA > 100 ng/mL individually, but not stated here. Results for longitudinal study: Showed that all patients with bone metastases had BALP > 30 ng/mL, whereas only 67% of patients with bone metastases had PSA > 100 ng/mL.
Comments: Unable to check the calculations of diagnostic values.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Comparator	Reference standards	Outcomes
Murphy et al (1997)								
70	Oct 1996 – Jan 1997	To investigate the usefulness of BALP, TALP, PSA, free-PSA and PSMA in the detection of bone metastases in patients with prostate cancer	Age 47–87 y. Patients suspected of having or known to have metastatic prostate cancer at initial diagnosis or during treatment. Sample: M0 = 47 M1 = 7 M2 = 8 M3 = 5 M4 = 3 Exclusion criteria not stated	Cross-sectional Case-series Unclear if consecutive (Although authors state that patients were 'evaluated in s sequential fashion', not clear whether this refers to a consecutive series.) Level IV	BALP (Tandem®-R Ostase) Patients had all tests. Not clear from papers whether test were compared independently of other tests or clinical information.	TALP % BALP PSA Free PSA % Free PSA PSMA	Bone scan Performed within 30 days of tests for markers Scan interpreted independently of patients' clinical status. Not clear whether tests interpreted independently of other test results.	ROC curves for BALP, TALP, free PSA individually. Values for area under curve measured individually for all tests. Used the cut-off values BALP 18 ng/mL & PSA 16 ng/mL to diagnose a positive bone scan; Sn: 56.5%, Sp: 65.9%. Mean value of BALP, TALP increased in relation to severity of disease. Mean value of PSA and PSMA no pattern.
Comments: Poorly written, insufficient data to check calculations of diagnostic accuracy values.								

Table 50 Prediction of fracture risk in peri/postmenopausal women without osteoporosis

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Ross et al (2000)								
512	Recruited in 1980 Mean follow-up 2.7 y	To assess the ability of selected bone formation and resorption markers and BMD to identify postmenopausal women who have an increased risk of osteoporotic fractures	Random sample chosen form the Honolulu Heart program. Age 43–80 y Community-dwelling 99% postmeno-pausal at time of first examination	Case series (cohort subgroup) Level IV	BALP (Ostase Tandem-R) Measured at baseline	CTx Calcaneus BMD	Fracture measured by self report (non-spine) or radiographs (spine)	Association between bone markers and BMD with fracture Odds ratio Calcaneus BMD; BALP (BMD-adjusted; BMD unadjusted) Spine: 1.49 (1.03, 2.16); 1.54 (1.12, 2.12); 1.88 (1.07, 2.07) Non-spine: 1.61 (1.05, 2.46); 1.88 (1.34, 2.65); 1.80 (1.27, 2.56) Either: 1.61 (1.20, 2.18); 1.53 (1.18, 1.98); 1.45 (1.11, 1.89) Probability estimates of fractures by multiple variable logistic regression analysis Probability fracture (%) BALP Z = 2 (BMD Z = –2, –1, 0, 1, 2): 33, 24, 17, 12, 8 BALP Z = 1 (BMD Z = –2, –1, 0, 1, 2): 26, 19, 13, 9, 6 BALP Z = 0 (BMD Z = –2, –1, 0, 1, 2): 20, 14, 9, 6, 4 BALP Z = –1 (BMD Z = –2, –1, 0, 1, 2): 15, 11, 9, 5, 3 BALP Z = –2 (BMD Z = –2, –1, 0, 1, 2): 11, 8, 5, 3, 2

Comments: Potential for selection bias. Extensive adjustment for potential confounders. The authors concluded that 'increased bone turnover is significantly associated with an increased risk of osteoporotic fracture in postmenopausal women. This observation is similar in magnitude and independent of that observed for BMD.'

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Garnero et al (2000)								
435	Recruited between February 1992 and December 1993 5-year follow-up	To test the hypothesis that decreased E_2 levels leading to increased bone turnover could play an important role in skeletal fragility in post-menopausal women	Taken from OFELY cohort Healthy postmenopausal women (>1 y) with no diseases or therapies affecting bone markers or hormones	Case series (cohort subgroup) Level IV	BALP (Tandem-R Ostase) Measured at baseline	Serum OC CTx Urine PICP PINP Dpy (free) NTx CTx	Fracture Peripheral or spinal (non-symptomatic spinal fractures identified by X-ray BMD measured at spine, femoral neck, distal radius and whole body by DEXA (Hologic QDR 2000) at baseline	79% had follow-up X-rays (mean 3.8 y; range 2.8–5.3) Risk of fractures *All patients after adjustment for age, prevalent osteoporotic fracture and physical activity* RR fracture (95% CI) *P* value Marker 4th quartile[a] >2 SD above mean (% women) BALP 2.4 (1.3, 4.2) 0.005 1.9 (1.13, 3.4) 0.03 (33%) [a] No significance for quartiles 1, 2 and 3 Model 1 Adjusted for age, prevalent osteoporotic fracture, physical activity and femoral neck BMD Model 2 Adjusted for age, prevalent osteoporotic fracture, physical activity and other hormones All at highest quartile RR fracture (95% CI) *P* value Marker Model 1 Model 2 BALP 1.9 (1.02, 3.4) 0.04 2.1 (1.1, 3.8) 0.02 *Patients restricted to those with non-vertebral or symptomatic vertebral fractures. Adjusted for age, prevalent osteoporotic fractures and physical activity* High risk cut-off is highest quartile RR fracture (95% CI) *P* value Marker Non-vertebral & symptomatic vertebral Non-vertebral BALP 2.5 (1.3, 4.7) 0.004 2.4 (1.1, 4.9) 0.026
Comments: Report concludes that 'high levels of some biochemical markers of bone turnover, low serum oestradiol, low DHEA sulfate, high SHBG (sex hormone binding globulin) and high PTH are associated with increased risk of osteoporotic fracture in postmenopausal women, independently of each other and of BMD.' Fracture incidence possibly underestimated as 21% of women did not have follow-up X-ray and therefore asymptomatic spinal fractures may not have been detected.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Garnero et al (1996)								
401	January 1992 – December 1993 Mean 22-month follow-up	To test the hypothesis that increased bone turnover (as measured by bone turnover markers) is a potential risk factor for osteoporotic fractures	Older women (aged >75) from EPIDOS cohort 126 women who sustained a hip fracture each matched with 2–3 controls matched by age and recruitment time. Also 144 premenopausal women – not included here	Nested case-control Level III-B	BALP (Tandem-R Ostase)	Serum OC Urine CTx NTx Dpy Measured at baseline	Hip fracture following moderate trauma	17/126 women with hip fracture excluded owing to therapy or disease known to affect bone metabolism. Prediction of fracture risk — OR (95% CI) Continuous: 1 SD increase; Categorical: T score > 2; *4th Q* BALP: 0.9 (0.8, 1.2); 1.0 (0.6, 1.6); 1.1 (0.7, 1.9) After adjustment for gait speed, CTx and Dpy remained significant. Correlations of femoral neck BMD with markers BALP: –0.18
Comments: Report concludes: 'the assessment of bone resorption with markers such as CTx or free Dpy may be useful to predict the subsequent risk of hip fracture in elderly women, in combination with hip BMD measurement.' No specific comments were made regarding BALP.								
Garnero et al (1999)								
305	OFELY Followed for 4 y	To examine the potential utility of bone markers to identify fast bone losers	305 postmenopausal women (>1 y) with no therapy or disease known to affect marker levels or BMD from the OFELY cohort who completed the 4-year study. 75 withdrew for personal reasons and 4 died	Case series (cohort subgroup) Level IV	BALP (Tandem-R Ostase) Measured at baseline	Serum OC PICP PINP CTx Urine CTx NTx	BMD measured by DEXA (Hologic QDR 2000 device) at baseline and years 2, 3 and 4. 97% of patients measured at all time points, four at 3 time points and four at one. All measured at 4 y.	High turnover defined as >2 SD from premenopausal mean. Accuracy of markers for predicting high bone turnover Mid-radius Marker: BALP; OR (95% CI): 1.80 (1.0, 3.2); Sn %: 39; Sp %: 79; PPV %: 48; NPV %: 71 Distal radius Marker: BALP; OR (95% CI): 1.61 (0.9, 2.8); Sn %: 36; Sp %: 77; PPV %: 44; NPV %: 71 Correlation (*r*) between BALP and BMD Marker: BALP; Mid-radius BMD: –0.14; Distal radius BMD: –0.11
Comments: Report concludes that 'increased levels of some of the biochemical markers of bone turnover are associated with greater radial bone loss.' These do not include BALP. Data not included for 79 women – 4 died but 75 withdrew for personal reasons. May have biased results. Only included women not on HRT or antiresorptive therapy, so may be generalisable only to untreated population.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Bauer et al (1999)								
295	SOF study Serum collected April–July 1989	To examine the ability of commercially available markers of bone turnover to predict hip bone loss	Postmenopausal women Subset of women aged >67 with no HRT from SOF Samples taken from 501; 89 excluded owing to oral E_2 use, 31 died before 2nd DEXA and 82 did not undergo 2nd DEXA.	Case series (cohort subgroup) Level IV	BALP (Tandem-R Ostase)	Serum OC Urine NTx CTx Dpy Pyr	BMD by DEXA (QDR 1000; Hologic Inc.) at baseline and after mean follow-up 3.8 y (range 3.3–5.1) Measured at total hip and 3 subregions (femoral neck, trochanter and intertrochanter)	Baseline Marker / *N* / Mean (SD) / Median / 4th Q BALP / 395 / 13.4 (7.1) / 11.6 / >15.0 Accuracy – above median (%) – total hip BMD Marker / Sn / Sp / PPV / NPV BALP / 59 / 46 / 35 / 69 Accuracy – above 4th Q (%) – total hip BMD Marker / Sn / Sp / PPV / NPV BALP / 29 / 74 / 36 / 68 Normal bone loss defined as <1.1% per year Correlations Marker / Total hip / Femoral neck / Troch / Inter-troch BALP / 0.08 / 0.00 / 0.05 / 0.12
Comments: Study concluded: 'biochemical markers have limited value for predicting rapid hip bone loss in individuals.' Intention to treat analysis not acted on – unclear why 82 patients who attended both visits did not have a 2nd BMD measurement. Strengths of study listed by the authors as (i) prospective, (ii) large number of subjects and long follow-up, (iii) careful measurement of bone mass and biochemical markers. Weaknesses listed as (i) single measurement of markers despite high day-to-day variability and (ii) BMD measured only at start and end-point; annual measurement may have better assessed bone loss.								

No of pts	Time period	Study aim	Population	Study type, level	New Test	Other tests	Reference standards	Outcomes
Chapurlat et al (2000)								
355	February 1992 – December 1993	To address the issue of the existence and magnitude of bone loss in pre- and perimenopausal women and the relationships of hormonal status with bone mass	Subgroup of the OFELY study. Included 355 women who were pre- or perimenopausal. 35 excluded (23 owing to disease and 12 owing to treatments), 8 had missing data and 40 (11%) were lost to follow-up. 76 classified as peri-menopausal (long cycles after previous normal cycles). 196 classified as premenopausal. Data extracted for perimenopausal women only.	Case series (cohort subgroup) Level IV	BALP (Tandem-R Ostase)	Serum OC PICP E_2 DHEA Testosterone SHBG FSH Urine NTx CTx 24-hour pregnanediol glucuronide	BMD by DEXA (QDR 2000; Hologic Inc) at baseline and 1-year intervals. Measured at the lumbar spine, femoral neck and trochanter.	Multiple regression analysis Baseline BALP and E_2 to predict femoral neck BMD showed $r^2 = 0.442$ and $P = 0.016$. Correlation (r) between bone loss and markers Marker: BALP; FN: –0.39; Trochanter: –0.03; Anterior posterior spine: –0.36 Explains only 15% of variance of bone loss at the individual level ($r = –0.39$).

Comments: Authors concluded: 'BALP and to a lesser extent urinary CTx were significant predictors of bone loss in perimenopausal women with increased FSH … In a multiple regression analysis of the determinants of bone loss, E_2 and BALP were independent predictors of bone loss. Increased bone turnover as assessed by BALP explained only 15% ($r = 0.39$) of the variance of the rate of loss and the markers at the individual level.'

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Cosman et al (1996)								
81	Recruited between 1988 and 1990. Studied over 3 y	To determine whether serum or urine biochemical markers of bone turnover can predict individual rates of hip bone loss	Recruited from local community through clinic and research centre Women: 17 premenopausal; 40 untreated postmenopausal (37.5% osteoporotic); 24 oestrogenised postmenopausal (83% osteoporotic)	Case series Level IV	BALP (Tandem-R Ostase)	Serum OC PICP TALP TRAP Urine Hyp Ca_2 Pyr Dpy Measured at baseline	BMD by DEXA (Lunar DP3, *n* = 33; or Hologic QDR-1000, *n* = 48) at 6-month intervals	Change in BMD Premenopausal – no significant change in hip or lumbar spine BMD. Untreated postmenopausal – significant absolute and percentage change in BMD of spine and hip. Oestrogenised postmenopausal – no significant change in hip BMD but small significant yearly gain in spinal BMD. Correlation of BMD change to biochemical markers Whole group Marker – Spine – Femoral neck BALP – –0.47 – 0.02 High-turnover (>SD from normal mean) patients were identified and BALP was found not to predict high bone turnover. Untreated postmenopausal Significant relationship between BALP and change in BMD lost. Multiple regression showed that BALP, Hyp, CP and Ca_2 were independent predictors of spinal BMD loss and could predict 42% of variance. Oestrogenised postmenopausal BALP not predictive of change in BMD in regression model. BMD losers BALP correlated with femoral neck bone losers (*r* between –0.32 and –0.44). Not correlated with spine losers.
Comments: The report concludes: 'measuring individual serum and urine levels in individual patients cannot accurately determine rates of bone loss in the spine and hip …. Even a combination of four variables (serum OC, BALP, and PICP and Hyp) in addition to readily available demographic variables (BMI and an estimate of calcium intake) could predict only 30–40% of variance in bone density change in both the spine and hip in postmenopausal, untreated women.'								

Table 51 Monitoring treatment for osteoporosis

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Bjarnason and Christiansen (2000)								
153	Not reported	To investigate the value of bone markers to predict the prevention of bone loss in early postmenopausal women on HRT	Recruited to HRT RCT (*n* = 278) by blinded, direct mail invitation using social security numbers Healthy, postmenopausal women (1–6 y); no medication affecting bone metabolism; no evidence of confounding diseases	Case series (subgroup of RCT) Level IV	BALP (Tandem-R Ostase) Measured at baseline, middle and end of cycle 1 and end of cycles 7, 13, 26 and 39	Serum OC CTx Urine CTx	BMD of lumbar spine (L2–4) and left femur by DEXA (Hologic QDR-2000) Measured at baseline and semi-annually throughout study.	Area under ROC curve (%) Absolute values / Change from baseline 6 months: 76.3 / 86.9 12 months: 84.4 / 92.6 Accuracy Cut-off / Sn / Sp / PPV / NPV ROC curve*: 20.6% / 85.5 / 80.0 / 92.2 / 66.7 ROC curve*: 7.3 µg/L / 55.5 / 90.0 / 93.8 / 42.4 conservative estimate: 44.5% / 36.4 / 97.5 / 97.6 / 35.8 conservative estimate: 5.4 µg/L / 29.1 / 97.5 / 97.0 / 33.3 Correlations(*r**) between BALP and response in spinal bone mass Absolute values / Change from baseline 6 months: 0.4 / 0.52 12 months: 0.52 / 0.64 24 months: 0.56 / 0.7 * approximated from graph
Comments: The authors concluded that 'early bone marker measurements predict long-term preservation of bone mass during HRT' and that 'resorption markers seem superior to formation markers.'								

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Dresner-Pollak (2000)								
90	Not reported 2-year follow-up	To examine whether early changes in BALP predict long-term changes in BMD in early postmenopausal women on HRT	Early post-menopausal women Natural *n* = 60 Postmenopausal < 12 months and FSH > 30 IU/mL Natural-menopausal women randomised to different combination HRT strategies Surgical *n* = 30 Hysterectomy or oophorectomy Surgical-menopausal patients given E_2 alone	Case series (subgroup of RCT) Level IV	BALP (Tandem-R Ostase) measured at baseline and 1, 3, 6, 12 and 24 months	None	BMD using DEXA (Norland XR-26 Bone Densitometer) measured at baseline and 6, 12 and 24 months.	63/90 (70%) completed 2-year study. Results Decrease in BALP level of 40% at 6 months; 56% sensitivity, 83% specificity, 95% PPV and 25% NPV in predicting spine BMD after 2 y of HRT. The ROC curve area under the curve was 0.604. Women with the greatest decrease in BALP (≥50%) at 6 months had the greatest increase in spine BMD at 2 y.
Comments: The report concludes that 'an over 50% decrease from baseline after 6 months of treatment suggests a positive skeletal response.' Only 70% of women completed the full study, and it is unclear how many were included in the analyses. Therefore, the results could be biased.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Delmas et al (2000b)								
569 Data from 2 RCTs	(Cooper 1999) *n* = 277 Dec 1993 – Nov 1996 2-year duration (Delmas et al 1999) *n* = 292 Not given; 2-year duration	To determine the utility of bone markers in the management of postmenopausal women receiving HRT	Natural or surgical menopause for 1–6 y	Case series (cohort from 2 RCTs of therapy) Level IV	BALP (Tandem-R Ostase)	Serum OC CTx (3 months) Urine CTx Measured at baseline and 3, 6, 12 and 18 months	BMD by DEXA (Hologic and Lunar densitometers) Measured at baseline and 6, 12, 18 and 24 months.	Only 388/569 patients analysed. Unclear why remaining patients were excluded. Initial analysis includes only BMD responders and non-responders; *n* = 299. Responders and non-responders only Area under ROC curve BALP vs 2-year BMD change at 3 and 6 months Combined 0.520 0.801 – Percentage 0.522 0.783 – Level 0.508 0.666 Correlation (*r*) 3 months and 6 months Marker % actual % actual BALP –0.07 –0.12 –0.43 –0.13 Accuracy of BALP (cut-off set so specificity is 90%) at 3 and 6 months Sn % PPV Cut-off Sn % PPV Cut-off Combined 11.0 0.825 63.6 0.857 Percentage 8.4 0.817 –20.08 49.4 0.887 –20.37 Level 8.6 0.822 17.8[a] 26.7 0.874 8.33[a] [a] ng/mL; All patients Accuracy (cut-off set so specificity is 90%) at 3 and 6 months Sn % PPV Cut-off Sn % PPV Cut-off Combined 8.2 0.781 44.3 0.831 Percentage 14.4 0.758 –20.1 41.9 0.833 –21.8 Level 8.2 0.769 1.83[a] 17.3 0.811 7.37[a] [a] ng/mLl
Comments: The authors wrote: 'our data suggest that the short-term change in bone markers reflects long-term changes in BMD in postmenopausal women with HRT'. Note that the overall analysis includes only 388 of the 569 patients randomised to the two studies, and the discrepancy is not explained by removing the placebo groups and/or patients with incomplete data. The main analysis was performed on a select group of patients who could be classified as responders or non-responders on the basis of BMD measurement. This excludes 89 of the 388 subjects in the overall analysis.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Marcus et al (1999)								
293	Randomised to treatments between Dec 1989 and Feb 1991	To assess the associations of 8 bone turnover markers with baseline and 1-year percentage changes in spine and hip BMD in women undergoing treatment with HRT	Taken from 3 centres of PEPI trial. Included 383 women; analysis includes 293 women who were at least 80% compliant and had complete data available. 212 women were available for 3-year analysis. Healthy postmenopausal women	Case series (subgroup of RCT of HRT) Cohort for prediction of BMD and treatment monitoring Level IV	BALP (Tandem-R Ostase)	Serum BALP (Alkphase-B) Serum markers measured at baseline and 12, 24 and 36 months Urine CTx NTx Pyr Dpy Urine markers measured at baseline and 12 and 36 months	BMD using DEXA (Hologic QDR 1000) measured at baseline and 12 and 36 months.	Treatment with active therapy resulted in a decrease in marker levels at 12 months but a return towards baseline at 36 months. Prediction of treatment response at 12 months (R^2; treatment groups; n = 239) Marker — Spine BMD — Hip BMD Resorption + formation (% Δ 0–12 months) ΔNTx + ΔBALP (Alkphase-B) — 0.103 — 0.042 ΔDpy + ΔBALP (Alkphase-B) — 0.095 — 0.043 ΔCTx + ΔBALP (Alkphase-B) — 0.104 — 0.041 ΔPyr + ΔBALP (Alkphase-B) — 0.096 — 0.042 Other combinations (BALP) — ≤0.092 — 0.033
Comments: With regards to the prediction of BMD and changes in BMD the report concludes that bone turnover markers are not useful surrogates to identify women of low bone mass and 'offer little useful information for predicting BMD changes for individual untreated or HRT-treated postmenopausal women''' Note that these analyses were presented for 1-year BMD loss. The authors stated that the associations with 3-year BMD data were even less.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Bjarnason et al (2001)								
2622	Recruitment started 1994 3-year follow-up	To study the relationship between the change in bone turnover and vertebral fracture risk in postmenopausal osteoporotic women on raloxifene	Subgroup of 7705 women from the MORE study Postmenopausal women with T-score < –2.5. Women with E_2-sensitive cancer or disease known to affect bone metabolism were excluded. Baseline characteristics of subgroup similar to MORE cohort. 2403/2622 had BALP data available.	Case series (subgroup of cohort study) Level IV	BALP (Tandem-R Ostase)	Serum OC Urine CTx Measured at baseline and 6, 12, 24 and 36 months	Vertebral fracture by spine radiographs at baseline and 24 and 36 months or if fracture suspected.	Analysis by tertiles of BALP and relative risk of new fracture *n* = 2403 Tertile (cut-off)[a] — RR — *P* value 1 (≤ 5.7) — 0.38 (0.22, 0.68) 2 (–5.7 < ≤ –1.9) — 0.74 (0.43, –1.25) — 0.036 3 > 1.9 — 1.05 (0.65, 1.70) [a] µg/L Multivariate analysis Pooled raloxifene (*n* = 1534) 87/1534 had fractures BALP unit — OR[a] — *P* value *6 months absolute change* –5.5 µg/L — 0.63 (0.50, 0.80) — <0.001 *12 months absolute change* –5.91 µg/L — 0.75 (0.62, 0.92) — 0.005 [a] Odds of suffering a new vertebral fracture for a 1 unit (SD) decrease in the variable
Comments: The authors concluded that their exploratory analysis showed that the 'change in bone turnover is related to fracture risk during raloxifene therapy' and stated that their study is the first to describe the relationship between changes in turnover during treatment and future fracture risk. High-quality, well-reported study.								

No of pts	Time period	Study aim	Population	Study type, level	New test	Other tests	Reference standards	Outcomes
Garnero (1999)								
307	Initiated in 1990 2-year follow-up	To develop a model based on the combination of a marker level and its percentage change at 6 months of therapy to predict long-term response in BMD	Women were part of an alendronate RCT (Liberman et al 1995). Only women on placebo and 10 mg/day alendronate were included. Women had to be at least 5 y post-menopausal and with a lumbar spine BMD T-score < –2.5.	Case series (subgroup of RCT) Level IV	BALP (Tandem-R Ostase) measured at baseline and 3, 6, 12 and 24 months	None	Lumbar spine BMD measured by DEXA (Hologic QDR-1000 measured at baseline and 2 y.	Multivariate regression model Level and change in BALP at 6 months vs spinal BMD at 2 y a b c d e *Level* –0.278±0.061 –0.294 ±0.064 –0.254 (< 0.001) *% change* –0.0655±0.0123 –0.343 ±0.064 –0.343 (< 0.001) *Both* 34% a, Regression coefficient ± SE; b, standardised regression coefficient ± SE; c, partial correlation coefficient; d, significance (*P* value); e, multiple regression coefficient (r^2) Accuracy of 6-month BALP at predicting 2-year BMD Assuming 90% specificity Model (cut-off) Sn PPV NPV Level (≤9.5 µg/L) 59 84 % change (≤38.2%) 61 83 74 Both (BALP level = 3.5%–0.24% change) 72 85 80 Correlation (*r*) of 6-month BALP to 2-year BMD Level –0.53 % change –0.54

Comments: The authors concluded that 'the combination of BALP level and of its percentage change after six months of treatment in a logistic model improved the prediction of the long-term BMD response to alendronate treatment compared with percentage BALP change alone.' However, they noted that as this was a post-hoc analysis, further studies are required.

Table 52 Existing systematic reviews

Research question	Search strategy	Databases searched	Inclusion and quality criteria	Quality rating of review
Nelson et al (2001)				
To examine the effectiveness of various strategies for diagnosing and monitoring postmenopausal women with osteoporosis. With respect to the MSAC review it examines the role of bone turnover markers in diagnosis and treatment management.	Relevant studies were identified using the following search strategy: 1. Exp osteoporosis Osteoporosis, postmenopausal 2. Bone density 3. 1 or 2 4. exp biological markers 5. genetic markers 6. marker$.tw 7. (bap or CTx or Dpy or NTx or Pyr).tw 8. 4 or 5 or 6 9. 3 and 7 10. limit 8 to human 11. limit 9 to English language 12. limit 10 to female 13. *looked at English abstracts of foreign articles* Cost-effectiveness papers were identified using the following search strategy: 1. exp osteoporosis 2. ec.fs 3. exp costs and cost analysis 4. cost allocation, cost-benefit analysis, cost control, cost of illness, cost sharing, health care costs, health expenditures 5. exp economics 6. costs and cost analysis; economic competition; economic value of life; economics, dental; economics, hospital; economics, medical; economics, nursing; economics, pharmaceutical; fees and charges; financial management; financial support; financing, organised; financing, personal; health care sector; inflation, economic; investments; medical indigency; taxes 7. 2 or 3 or 4 8. 1 and 5 9. limit 6 to English language 10. *looked at English abstracts of foreign articles*	Medline (1966–2000) HealthStar (1975–2000) Reference lists of systematic reviews were checked and local and national experts were contacted. Manufacturers of bone measurement tests were contacted for performance data but no new data were received.	***Study design:*** Any clinical study (case reports excluded) ***Patients***: Women with or at risk of postmenopausal osteoporosis ***Tests:*** Biochemical bone formation and resorption markers, including TALP, BALP, OC, PICP, PINP, Hyp, Ca_2, Pyr, Dpy, CTx, NTx, TRAP ***Reference standard:*** BMD ***Outcomes:*** Diagnostic accuracy, prediction of fracture, bone loss, treatment response ***Quality criteria:*** Used criteria developed by the Third US Preventive Services Taskforce. Includes a description of a set of minimal criteria for each study design and results in ratings of good, fair and poor. Economic evaluations were assessed using six principles adapted from Udvarhelyi et al (1992). ***Application of methods***: Two investigators reviewed titles and abstracts to determine need for full review and to determine study eligibility. Data were extracted by lead investigator and any difficulties were examined by a second reviewer.	1) Are any inclusion/exclusion criteria reported related to the primary studies which address the review question? yes 2) Is there evidence of a substantial effort to search for all relevant research? yes 3) Is the validity of included studies adequately assessed? yes 4) Is sufficient detail of the individual studies presented? yes 5) Are the primary studies summarised appropriately? yes

Results

Use of biochemical markers instead of BMD to identify women with low bone density

Five cross-sectional studies were available. Although BALP correctly identified 70% of patients with osteoporosis, 42% of women with high levels did not have osteoporosis. The predictive value was 21%. The report concluded that no single marker or cluster of markers accurately identified people with osteoporosis as measured by BMD.

Do markers predict fracture?

Three prospective studies and three nested case-control studies. The results of the EPIDOS study showed that BALP was not a significant predictor of fracture. The report concluded that no marker was associated with increased fracture risk, and that although the EPIDOS study suggests that using markers with BMD increases predictability, no other studies have confirmed this.

Can markers help select patients for treatment?

Eleven longitudinal studies show the association between mean group marker levels and rates of bone loss measured by BMD at follow-up. In the Study of Osteoporotic Fractures BALP was not significantly correlated with DEXA. One of three studies examining BALP found a significant correlation with bone loss. The report concluded that there was no clear trend between markers and bone loss and that sensitivity and specificity were too low to be useful in selecting patients for treatment. Some studies showed improved accuracy when two or more markers were used in combination.

Can markers predict response to therapy?

Six longitudinal studies for prediction of response to alendronate. Four studies compared BALP to spine DEXA at 12–30 months and the correlation coefficient was –0.06 to –0.67; three were statistically significant. Hip DEXA (two studies) and total body and wrist DEXA were not significantly associated with BALP.

Eleven studies prospectively studied prediction of response to HRT. One study showed that BALP at 6 months had 56% sensitivity, 83% specificity, 95% PPV and 25% NPV in predicting gain in BMD at 2 years. There was no association between hip DEXA and % change in BALP. In another study BALP at 3 and 6 months was shown to be correlated with DEXA at 2 years. BALP was shown to be inaccurate at 3 months but slightly improved at 6 months. In another study where cut-offs were set to keep false positive rates low, sensitivity was low for BALP. The report concludes that there is a small correlation between markers and DEXA but they are not reliable enough to predict response in individual patients. The best results in the EPIDOS study have not been replicated.

Study type listed as II-2 – III: poor-fair to poor-good.

Comments: High-quality, systematic review. The BALP results can be applied to the MSAC review.

Research question	Search strategy	Databases searched	Inclusion and quality criteria	Quality rating of review
Smith and Greer (2001)				
Not stated	Not reported	Medline (dates not reported) Premedline (dates not reported) Bibliographies of identified studies Expert input	Not reported	1) Are any inclusion/exclusion criteria reported related to the primary studies which address the review question? no 2) Is there evidence of a substantial effort to search for all relevant research? unclear 3) Is the validity of included studies adequately assessed? no 4) Is sufficient detail of the individual studies presented? yes 5) Are the primary studies summarised appropriately? yes

Results:

The conclusions of the review were as follows:

1. Biochemical markers of bone turnover are safe and minimally invasive.
2. It is not possible to predict an individual's fracture risk using bone markers.
3. Bone markers are not sufficiently accurate to be used to diagnose osteoporosis.
4. Several marker levels respond to therapy, but there is no conclusive evidence that they could be used to help select therapies or predict BMD response in individual patients.
5. There are no studies which look at the role of biochemical markers in improving treatment compliance.

Comments: Few details of methodology provided. Includes same studies as current review.

Appendix D Correlation results

Eleven studies provided results only of the correlation between BALP (as measured by Ostase) and BMD (Table 53). Two studies examined the role of biochemical markers in predicting bone loss after menopause (Rogers, Hannon, & Eastell 2000) or inflammatory bowel disease (Dresner-Pollak et al 2000), and nine examined the role of markers in treatment monitoring (Biermasz et al 2001; Bone et al 2000; Garnero et al 1994; Hall, Spector, & Delmas 1995; Hodsman et al 1997; Kress et al 1999a; Kyd et al 1998; Watts & Becker 1999; Westeel et al 2000). Most studies (with the exception of that carried out by Westeel et al (2000) and Dresner-Pollak et al (2000)) were in postmenopausal women. The study by Westeel et al (2000) examined the effect of cyclosporine on steroid-induced osteopenia in patients undergoing a kidney transplant, and the study by Dresner-Pollak (2000) looked at the risk of bone loss in patients with inflammatory bowel disease. The study characteristics and results of the correlation analyses are briefly summarised below. Note that the methodological quality of these studies has not been assessed.

Table 53 Correlation results of excluded studies

Study	N[a]	Comparison		Correlation (*r*)
Fracture risk				
Rogers et al (2000)	60	BALP (baseline)	BMD (% change/year)	–0.43
Dresner-Pollak et al (2000)	36	BALP (baseline)	LS and FN BMD (2-year change)	No significant correlation
Treatment monitoring				
Kress et al (1999a)	222	BALP (% change 0–3 months)	LS BMD (1-year % change)	–0.43[b]
		BALP (% change 0–6 months)	LS BMD (1-year % change)	–0.49[b]
Hall et al (1995)	106	BALP (baseline or after 3 months' treatment)	LS BMD (baseline or 2-year change)	No significant correlation
Overgaard et al (1996)	Unclear	BALP (change 0–3 months)	BMD (2-year change)	Significant correlation
		BALP (change 0–12 months)	BMD (2-year change)	Significant correlation
Kyd et al (1998)	35	BALP (% change 0–6 months)	LS BMD (1-year % change)	–0.24
		BALP (% change 0–6 months)	FN BMD (1-year % change)	–0.09
Watts and Becker (1999)	25 (24)	BALP (change)	BMD (% change/year)	No correlation
Hodsman et al (1997)	30	Bone formation markers (change 0–3 months)	BMD (change 2 y)	–0.13 to –0.29
Garnero et al (1994)	85 (84)	BALP (% change 0–6 months)	BMD (% change 2 y)	–0.77
Biermasz et al (2001)	18	BALP (% change 0–6 months)	BMD (% change 1 y)	–0.68
Westeel et al (2000)	52 (40)	BALP (change 0.5–6 months)	BMD (Z score change 3–24 months)	0.40

[a] Values in parentheses denote number available for analysis of BALP vs BMD.
[b] Combined treatment and control groups.

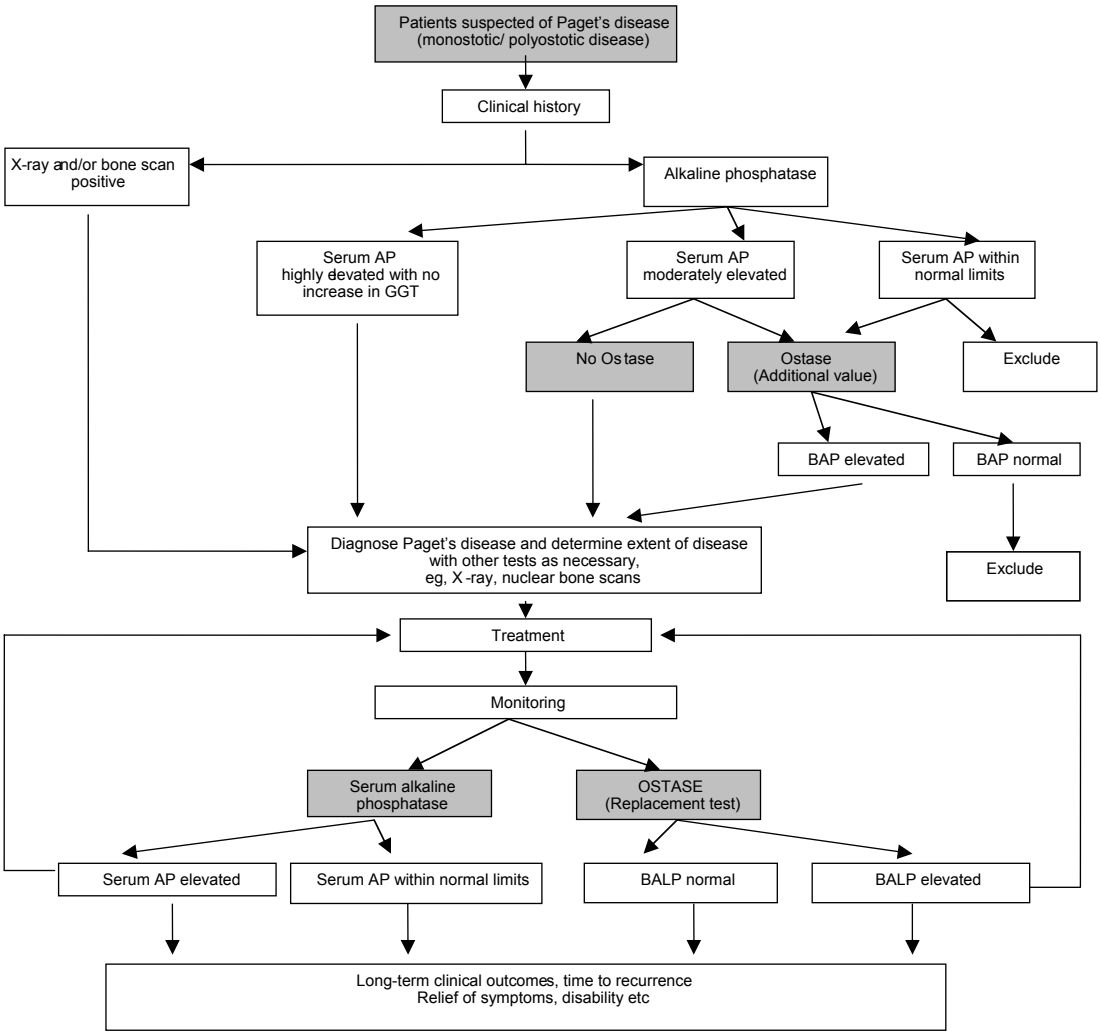
Appendix E Clinical questions

Table 54 Clinical questions for each of the indications

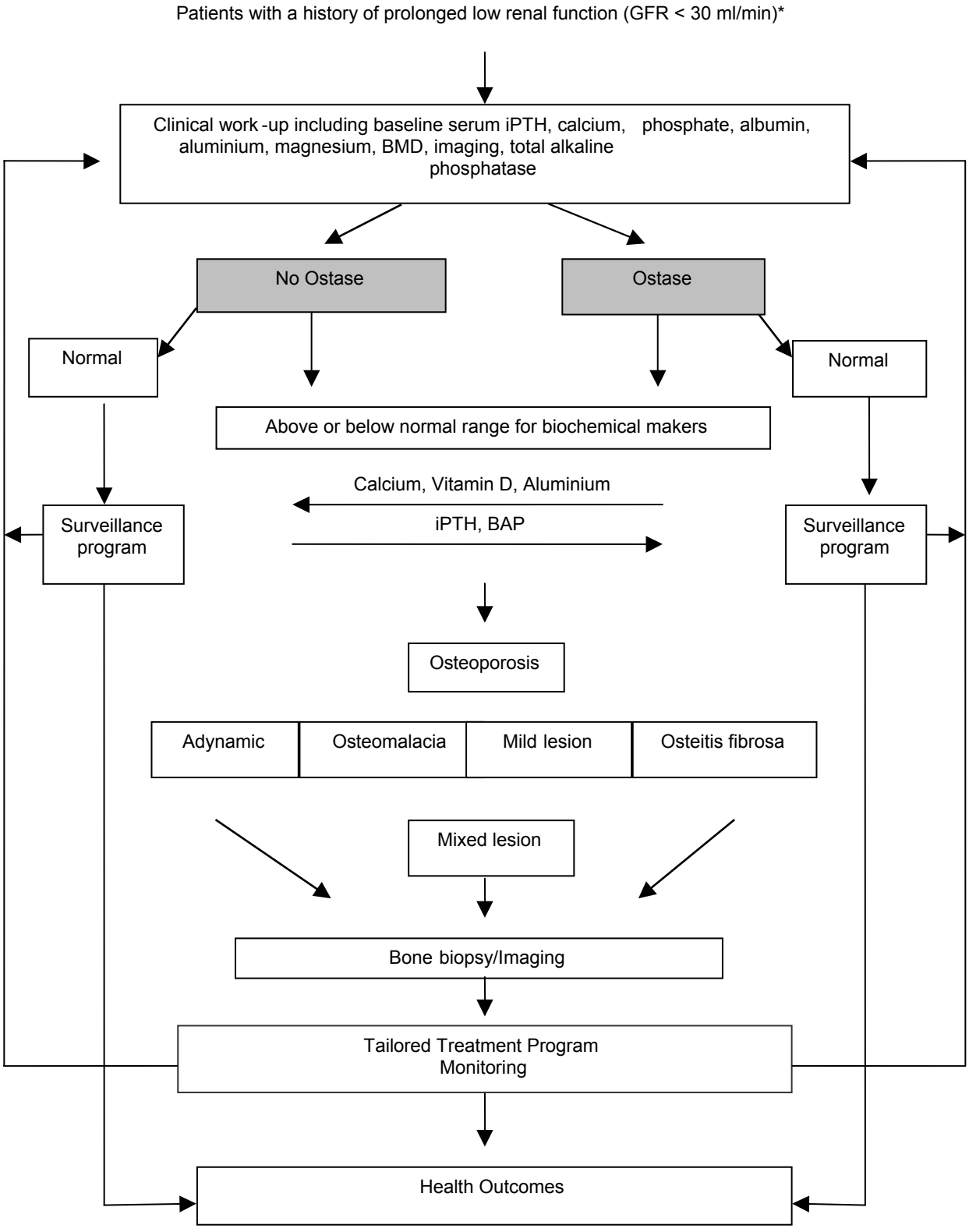
Patients	Intervention	Comparator	Outcomes	Reference standard
1. Patients suspected of having Paget's disease of bone (especially patients with moderate or normal TALP levels) 2. Patients who have received treatment for Paget's disease of bone.	Ostase 1. Diagnostic work-up 2. Treatment monitoring	1. Incremental to TALP 2. Replacement for TALP	• Diagnostic accuracy • Change in patient management • Change in patient health outcomes	1. Bone scans, X-rays 2. Long-term clinical outcomes, time to recurrence, relief of symptoms
Patients with renal osteodystrophy	Ostase Differentiation of the different patterns of bone disease Monitoring of therapy • Dialysis • Calcitriol therapy • Renal transplantation • Parathyroidectomy	Incremental to other biochemical makers	• Diagnostic accuracy • Change in patient management • Change in patient health outcomes	Bone biopsy, imaging
1. Patients without bone metastases of prostate cancer newly diagnosed or undergoing treatment 2. Patients with bone metastases undergoing treatment	Ostase 1. Diagnosis of bone metastases 2. Treatment monitoring	Incremental to PSA and TALP	• Diagnostic accuracy • Change in patient management • Change in patient health outcomes	1. Bone scans, X-rays 2. Pain relief, long-term clinical outcomes
1. Patients at risk of osteoporosis or osteopenia 2. Patients treated to prevent or reduce osteoporosis	Ostase 1. Assessment of fracture risk to inform treatment decision 2. Assessment of response to treatment	Incremental to DEXA or other biochemical markers	• Diagnostic accuracy • Change in patient management • Change in patient health outcomes	BMD (DEXA) Fracture

Appendix F Clinical flow charts

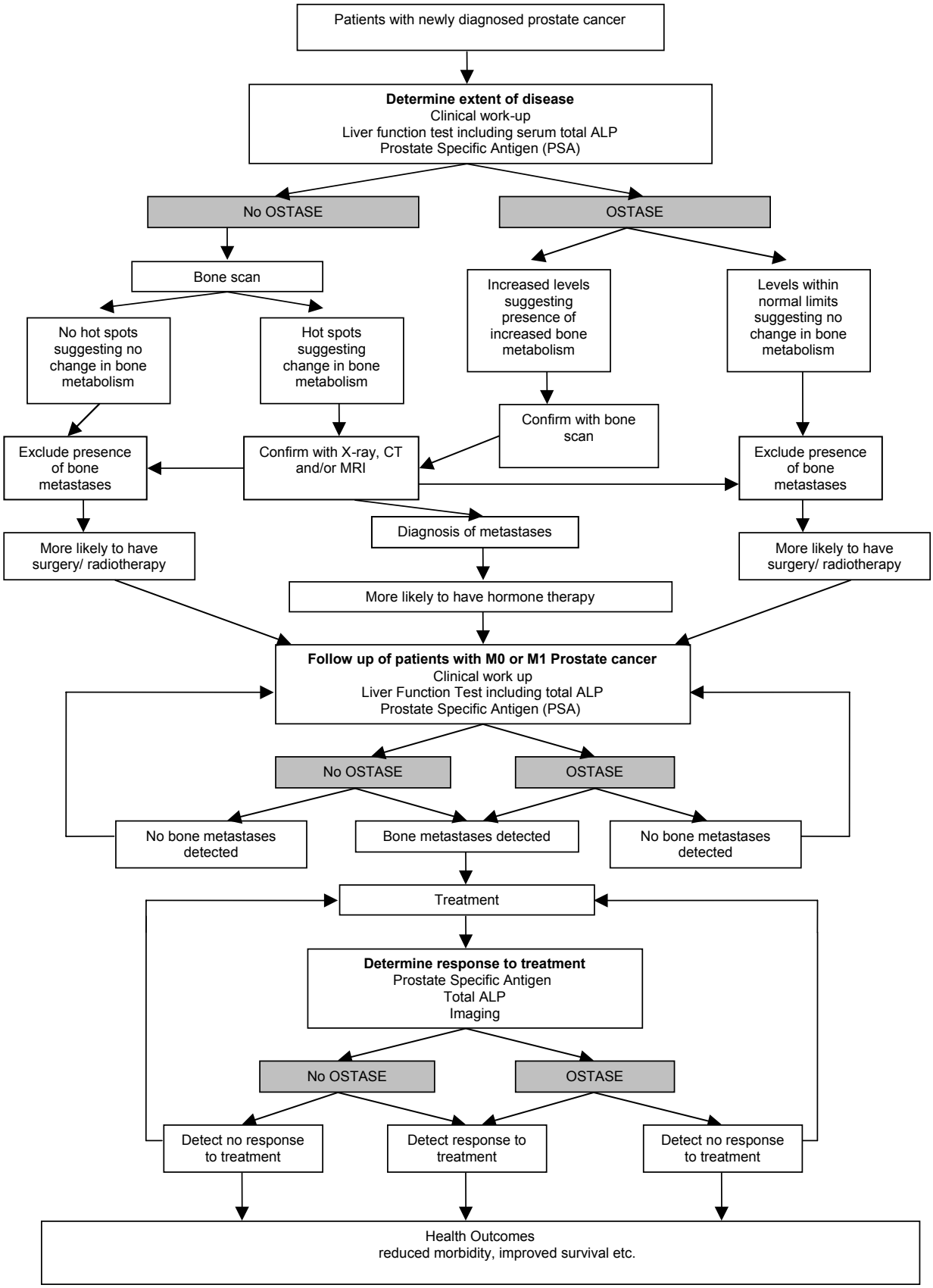
Paget's disease of bone



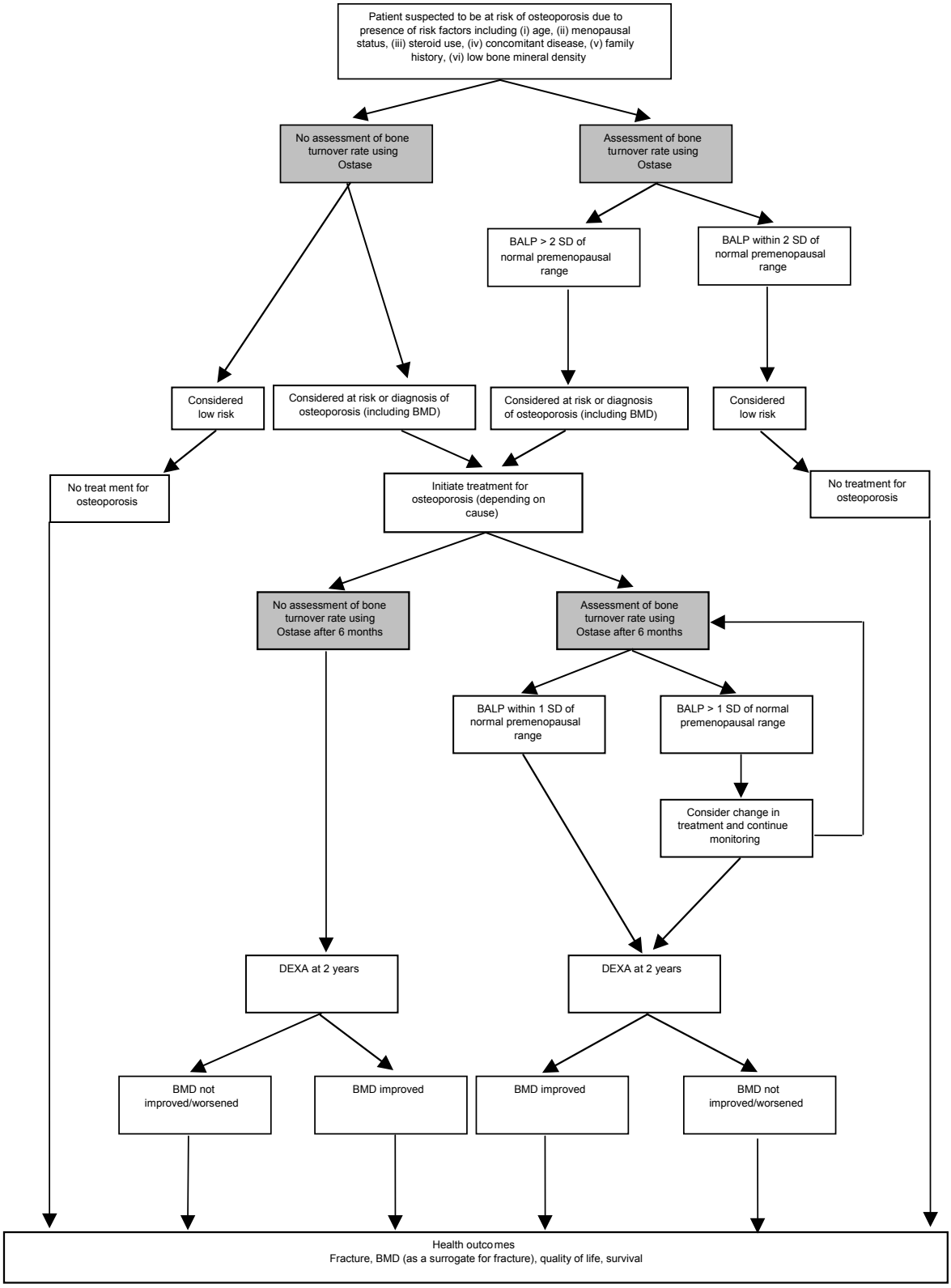
Renal osteodystrophy



Bone metastases in prostate cancer



Osteoporosis



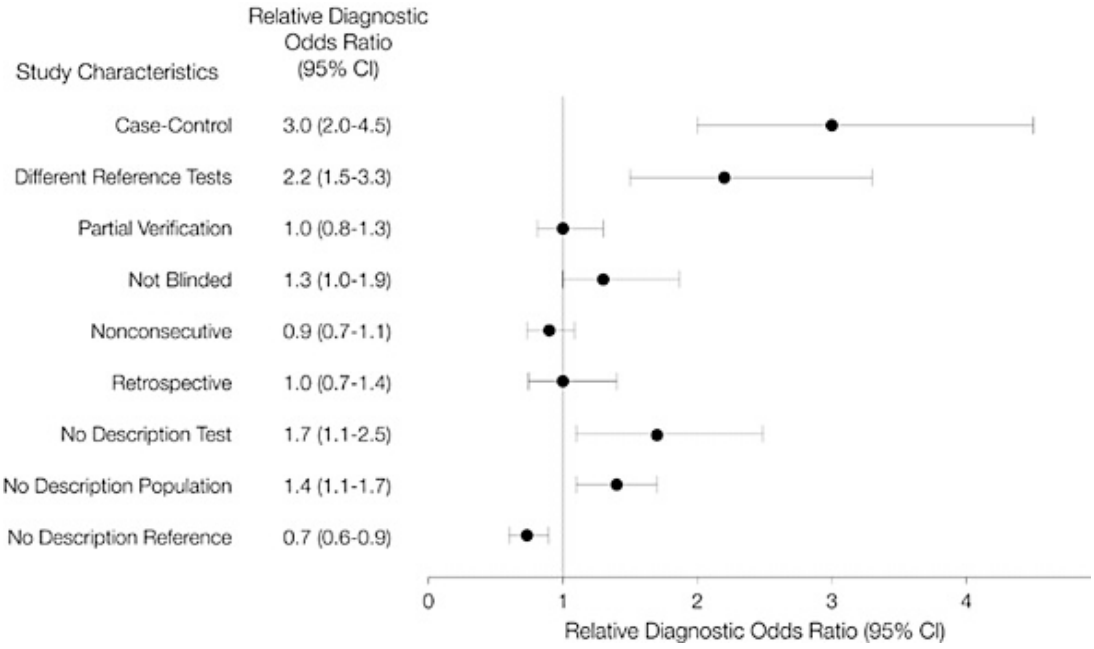
Appendix G Potential methodological biases in diagnostic test studies

Lijmer et al (1999) conducted an observational study of the methodological features of 184 original studies evaluating 218 diagnostic tests. The authors empirically assessed the impact of shortcomings in design and data collection of diagnostic studies in relation to the estimates of diagnostic accuracy. Overall, the results suggested that the diagnostic accuracy of a test was overestimated in studies:

- with a case-control design
- using different reference tests for positive and negative results of the index test
- accepting the results of observers who were unblinded to the index test results when performing the reference tests
- that did not describe diagnostic criteria for the index tests
- in which participants were inadequately described.

Interestingly, non-consecutive selection of patients resulted in a slight underestimation of accuracy, and retrospective data collection was not associated with an overestimation or underestimation of diagnostic accuracy in comparison with studies with prospective or unknown data collection.

Relative diagnostic odds ratios and 95% confidence intervals (CIs) of nine study characteristics examined by multivariate regression analysis (Lijmer et al 1999).



Appendix H Abbreviations

ABD	adynamic bone disease
Acc	diagnostic accuracy
Al	aluminium
AUC	area under the curve
BALP	bone alkaline phosphatase
BMD	bone mineral density
BMI	body mass index
BPH	benign prostate hyperplasia
$(Ca_3(PO_4)_2$	calcium phosphate
CI	confidence interval
Cr	serum creatine
CT	computed tomography
CTx	carboxy-telopeptide of type 1 collagen
DEXA	dual-energy X-ray absorptiometry
DHEA	dehydroepiandrosterone
Dpy	deoxypyridinoline
E_2	oestrogen
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FDA	United States Food and Drug Administration
FN	femoral neck
FSH	follicle-stimulating hormone
GFR	glomerular filtration rate
HOS	Hawaii Osteoporosis Study
HPT	hyperparathyroidism

HRT	hormone replacement therapy
HTBD	high-turnover bone disease
Hyp	hydroxyproline
ICMA	electrochemiluminescence immunoassay
ICSI	Institute for Clinical Systems Improvement
ICTP	carboxy-propeptide of type 1 collagen
iPTH	intact parathyroid hormone
IRMA	immunoradiometric assay
LALP	liver alkaline phosphatase
L-BALP	lectin precipitation method for bone alkaline phosphatase
LS	lumbar spine
LTBD	low-turnover bone disease
MBS	Medicare Benefits Schedule
MO	mixed osteodystrophy
MORE	Multiple Outcomes of Raloxifene Evaluation
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NPV	negative predictive value
NTx	amino-telopeptide of type 1 collagen
OC	osteocalcin
OF	osteitis fibrosa
OR	odds ratio
PEPI	Postmenopausal Estrogen / Progestin Interventions study
PICP	carboxy-terminal propeptide of type I collagen
PINP	amino-terminal propeptide of type 1 procollagen
PPV	positive predictive value
PSA	prostate-specific antigen

PSMA	prostate-specific membrane antigen
PTH	parathyroid hormone
Pyr	pyridinoline
RCT	randomised controlled trial
RIA	radioimmunoassay
ROC	receiver operator characteristic
RR	relative risk
SD	standard deviation
SEM	standard error of the mean
SHBG	sex-hormone-binding globulin
SHPT	secondary hyperparathyroidism
Sn	sensitivity
SOF	Study of Osteoporotic Fractures
Sp	specificity
TALP	total alkaline phosphatase
TRAP	tartrate-resistant acid phosphatase
ULN	upper limit of normal

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