Authors' objectives

To assess the effectiveness of various strategies for diagnosing and monitoring postmenopausal women with osteoporosis. The review aimed to address the following six specific questions.

1. What is the role of clinical risk factors, alongside testing, in identifying high-risk individuals and guiding treatment?
2. What are the advantages and disadvantages of bone measurement tests for identifying high-risk individuals?
3. Are bone measurement tests effective for monitoring response to treatment?
4. Are biochemical markers of bone turnover effective for identifying individuals at risk of bone loss, guiding treatment, or monitoring response?
5. What tests are appropriate for evaluating patients with osteoporosis for secondary causes?
6. What are the costs and cost-effectiveness of various diagnostic strategies? (Not addressed in this abstract.)

Searching

MEDLINE (1966 to 2000) and HealthSTAR (1975 to 2000) were searched for relevant articles; the search strategies were presented in full in an appendix to the report. Additional studies were sought by checking the reference lists of systematic reviews, and by contacting experts in the field and the manufacturers of bone density measurement tests. All searches were limited to English language publications.

Study selection

Study designs of evaluations included in the review

Case reports were excluded. No specific inclusion criteria for the study design were reported.

Specific interventions included in the review

For question 1, studies were included if they specified methods for measuring risk factors. Randomised controlled trials (RCTs) of interventions were not included.

For questions 2 and 3, Studies of bone density and quantitative ultrasound tests were included. Studies of single- and dual-photon absorptiometry were excluded.

For question 4, studies of biochemical markers of bone turnover were included.

For question 5, no clear inclusion criteria were specified.

Reference standard test against which the new test was compared

For questions 1, 2 and 3, studies were included if they reported relationships between the test or risk factor under consideration and bone measurement test results, bone loss, or fracture at any site.

For question 4, studies of biochemical markers of bone turnover were required to use bone densitometry as the reference standard.

For question 5, no clear inclusion criteria were specified.

Participants included in the review

Studies of postmenopausal women were eligible for inclusion. Studies in patients using steroids were excluded. Studies...
of patients with serious conditions (i.e. transplant recipients, in-patients, and those with other known secondary causes of osteoporosis) were excluded.

Outcomes assessed in the review
For question 1, 4 and 5, no clear inclusion criteria were specified.

For questions 2 and 3, studies were included if they reported sufficient data to construct a cross-tabulation of fracture status with test result. Studies of agreement between different densitometry methods were included if they provided information on how the use of different tests affected patient classification, using T- or Z-scores.

How were decisions on the relevance of primary studies made?
Two reviewers assessed titles and abstracts to select articles for full-text review. Any disagreements were resolved by the lead investigator for the topic. Investigators examined the full-text versions of retrieved articles and re-applied the inclusion criteria.

Assessment of study quality
Criteria specific to each of the study designs included in the review were used to assess study quality and to classify the included studies as 'good', 'fair' or 'poor'. These criteria were reported in full in an appendix to the report.

Prospective cohort studies and RCTs were assessed for the following: baseline comparability of the study groups, follow-up rate, description of the interventions, appropriateness of outcome measures, consideration of confounding factors, and use of intention-to-treat analysis (for RCTs).

Diagnostic accuracy studies were assessed for: inclusion of an appropriate spectrum of participants, use of an appropriate reference standard, independence of the index test and reference standard, assessment of test reliability, and handling of indeterminate test results.

Case-control studies were assessed for: appropriate ascertainment of cases and selection of participants, equality of application of exclusion criteria to cases and controls, equality in application of tests to cases and controls, response rate, and treatment of confounding variables.

The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
All data were extracted by the lead investigator for the topic. If the lead investigator encountered difficulties, a second investigator was consulted and consensus reached. Information on the study population, interventions, clinical end points, study design and study quality was extracted.

Methods of synthesis
How were the studies combined?
The results of the studies were combined in a narrative, organised by topic or research question.

How were differences between studies investigated?
No formal assessment of between-study heterogeneity was reported. The studies were grouped within a topic or research question by intervention, and there was limited discussion of the differences between studies within the text (e.g. in terms of study quality grading in some sections of the results).

Results of the review
Question 1: a total of 45 studies addressed risk factor assessment. Seventeen studies (n=61,996) assessed factors predicting hip fracture, 8 studies (n=28,214) assessed factors predicting low bone density, 4 studies (n=4,016) assessed factors predicting bone loss, and 17 studies assessed the use of risk assessment tools.
Questions 2 and 3: 9 studies assessed bone measurement tests for the prediction of fracture, and 26 studies assessed agreement between different bone measurement tests.

Question 4: a total of 45 studies assessed biochemical markers of bone turnover. Five studies (n=1,427) assessed the diagnostic accuracy of biochemical markers in comparison with bone density, 6 studies (n=1,994) assessed the ability of markers to predict fracture in untreated individuals, 12 studies (n=1,522) assessed the ability of markers to predict bone loss in untreated individuals, and 18 studies examined the use of markers to monitor or predict response to therapy (n>2,974).

Question 5: no studies were found.

Question 1.

Factors consistently associated with increased risk of low bone density and fracture were increasing age, white race, low weight or weight loss, non-use of oestrogen replacement, history or family history of fracture, history of falls, and low scores on measures of physical activity or function. Other risk factors, which were statistically significant in some studies, were smoking, alcohol use, caffeine use, low calcium and vitamin D intake, and some drugs. Predictors of low bone density were similar to those for fracture. Some risk factors were as powerful as bone density in predicting hip fracture. People with multiple risk factors and low bone density have a particularly high risk of hip fracture.

There were few studies evaluating the use of risk factors to identify women at risk for fracture, and the accuracy of methods designed to assess the risk factors was generally poor.

No studies were identified that compared treatment decisions based on clinical risk factors with those based on bone measurement tests or a combination of the two.

Questions 2 and 3.

Bone density measured at the femoral neck by dual energy X-ray absorptiometry was the best predictor of hip fracture. It was comparable to forearm measurements for predicting other fractures. More recent studies of quantitative ultrasound measured at the heel showed comparable results. Individuals with high scores on one test and low scores on the other had intermediate probability of fracture.

Correlations between different bone measurement methods were generally low.

The likelihood of a diagnosis of osteoporosis varied with type of bone measurement test, brand of densitometer, relevance of reference range to local population, and number and location of sites tested. The results were often inaccurately reported to the patients.

One RCT suggested that women undergoing densitometry were more likely to start hormone replacement. One trial and one case series found that women who had undergone densitometry and who had been told that they had osteoporosis were more likely to start or continue hormone replacement. In one trial physicians found densitometry reports confusing and were not confident of their interpretations.

Evidence did not support repetition of bone density tests within the first year of treatment. There was insufficient evidence to determine the usefulness of repeating after two years of treatment. No studies assessing the effect of monitoring response to therapy, or choice of test on therapy outcome, were identified.

Question 4.

No single marker or combination of markers was accurate in predicting the results of bone densitometry. No marker could accurately predict increased fracture risk. One study suggested that using markers in combination with densitometry resulted in a more accurate prediction of fracture. Marker results did not correlate with bone loss. Some studies found better accuracy where markers were used in combination with other markers or risk factors to predict bone loss.
The accuracy of markers was too low to be useful in selecting patients for treatment. There was a small correlation between response to therapy (measured by densitometry) and marker results, but no marker was sufficiently accurate to identify individuals who will fail to respond to treatment.

Question 5.

There was no evidence on which to base the formulation of a strategy to determine secondary causes of osteoporosis.

Cost information
The report contained cost-effectiveness modelling.

Authors' conclusions
Data applying the results of epidemiological studies to diagnosis and monitoring in clinical settings were sparse or lacking for most of the questions addressed by the review. Future research should focus on application to the clinical setting.

CRD commentary
The review set out to address a number of clearly stated research questions pertinent to the diagnosis and monitoring of osteoporosis. However, the inclusion criteria were poorly defined and were not reported clearly. The restriction of the search strategy to two databases and to studies published in English might have resulted in the loss of some relevant data. Publication bias was not assessed. Appropriate measures were taken to avoid the introduction of error and/or bias when initially selecting studies from titles and abstracts. However, it was unclear how the full-text versions of retrieved articles were treated, and the data extraction was performed by one reviewer; the review process therefore remains vulnerable to the effects of error and/or bias. A detailed description of the quality assessment was provided in the 'Methods' section of the report, but the results of this were not reported in full or used consistently in the narrative synthesis. Full evidence tables were reported in an appendix to the report, but the narrative synthesis presented in the 'Results' section lacked structure and comparative numerical data, and was difficult to interpret. The authors' conclusions appear appropriate given the lack of evidence presented, but should be treated with caution in light of the limitations outlined.

Implications of the review for practice and research
Practice: The authors made no specific recommendations for practice.

Research: The authors made the following recommendations for future research.

Future studies should focus on the application of epidemiological data to clinical settings, and should include more diverse groups of participants.

Prospective studies of risk factor assessment tools are needed to determine whether such tools can correctly stratify risk, influence treatment, and improve outcome.

Clinical trials are required to determine if identifying and reducing modifiable risk factors can improve outcome.

RCTs are needed to determine whether overall fracture risk is a better predictor of benefit from therapy than bone measurement alone. Trials should also address whether patients shown to have bone loss by different techniques at different sites demonstrate a similar treatment benefit to those identified by hip absorptiometry.

Research is needed to identify patient information needs.

Future research should examine the utility of the World Health Organization criteria for diagnosing osteoporosis.

High-quality, prospective studies of biochemical markers are needed to define, apply, and evaluate criteria for their use.
in clinical decision-making.

The utility of screening for secondary disorders using common laboratory tests should be tested in large cohort studies or treatment trials of osteoporosis.

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