**INAHTA Joint Project**

# Bone Density Measurement and Treatments of Osteoporosis

## Statement of findings - summary

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The statement has been endorsed by the following organisations which are members of the International Network of Agencies for Health Technology Assessment (INAHTA):

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**Summary**

**Objective**: To provide a summary of the available scientific evidence on the performance of bone density measurement (BDM) techniques and the effectiveness of BDM screening and related interventions - hormone replacement therapy (HRT) and intranasal salmon calcitonin SCT(N)) - in menopausal women to prevent fractures in later life.

**Methods**: Synthesis of systematic reviews of evidence on BDM, HRT and SCT(N) updatted by primary studies identified through additional literature searches. The evidence was evaluated using an internationally accepted classification system incorporating study design and quality.

**Main Findings**: The analytical performance of BDM technologies in the routine clinical situation has not been adequately assessed. Fair evidence from prospective cohort studies suggests that BDM can predict the risk of fractures, though not with high accuracy. Although good evidence exists to support the efficacy of HRT and SCT(N) in preserving bone mass during treatment, there is also fair evidence that the effect wears off after cessation of therapy. Fair evidence, from low quality RCTs and observational studies, suggests that these therapies are efficacious in preventing fractures. However, when this evidence is used to evaluate the potential effectiveness of BDM screening of menopausal women in combination with these therapies it is estimated, using realistic assumptions, that only 1-7% of hip fractures might be prevented.

**Conclusion**: The currently available evidence does not support the use of BDM screening in combination with HRT or SCT(N) treatment.

## Introduction

Osteoporosis predisposes women to bone fractures that occur most commonly at the hip, wrist and spine. Hip fractures are of particular concern because of their high costs in terms of morbidity, mortality and social burden.

Consequently, there is growing international interest in approaches to identify individuals at high risk for fractures and in interventions that might help to prevent these events. Various techniques to measure bone density have been developed for detecting those at high risk of having a fracture. These individuals are commonly prescribed treatments in the form of hormone replacement therapy (HRT), and in some Mediterranean countries, calcitonin (CT).

## Scope

This review has been produced through a collaboration between national and regional agencies which undertake health technology assessment.

- The objective is to assess the available scientific evidence regarding the performance of bone density measurement (BDM) and its effectiveness in preventing fractures when used in conjunction with prophylactic treatments (HRT and intranasal salmon calcitonin) in menopausal women.
- The main outcome measures are bone density and fractures. Evaluation is in terms of the relative risk of fracture for a 1 SD decrease in bone mineral density below the age adjusted mean; the percentage of fractures potentially prevented by BDM screening linked to treatments; and the number of individuals who would need to be invited for screening in order to prevent one hip fracture. Treatment effects of HRT and SCT(N) for preserving bone density are expressed as relative risks or odds ratios for fractures.
- This paper does not assess other approaches to identify individuals at high risk for fracture nor any alternative interventions such as exercise, hip protector pads, vitamin D and bisphosphonates. The impact of BDM and associated treatments is considered only in terms of their effect on the risk of fractures in women.

## Methodology

This paper is based primarily on systematic reviews of evidence undertaken by health technology assessment agencies and other systematic reviews that were relevant. These sources were updated by adding primary studies identified through additional literature searches. The search for relevant research was supplemented by two surveys of organisations that had produced reports addressing the issues of BDM and HRT.

The conclusions in this paper are based on a classification system that considers the type of study design and conditions of scientific rigour (Table 1). Further details about the methodology are available in the background documents.

## Results

### 1. Methods for Bone Density Measurement

**1.1 Various methods are currently used for measuring bone density, but x-ray based methods dominate the market. Ultrasound methods are increasingly used, but their analytical performance still requires validation.**

**1.2 The precision and accuracy of BDM technologies are generally poorly defined in the routine clinical situation for all available methods.**

Table 2 describes the performance characteristics of BDM methods in common use. Most available data are from measurements taken in a single centre over a short period by expert operators. Consequently, they tend to reflect the efficacy of the individual methods, and are likely to underestimate the error in routine clinical practice.

**1.3 The performance characteristics of BDM methods impose constraints on specific applications of these techniques.**

Given the performance levels of currently available methods, many individuals will be wrongly classified with regard to their risk of fracture, either as false positives or false negatives. This problem is compounded by systematic differences in 'normal' values in population (e.g. ethnic groups) from those used to set reference values for BDM equipment.

**1.4 If bone density measurements are to be undertaken, it is essential that scrupulous quality control is followed.**

**2. The use of BDM to predict fractures in individuals** (2)

**2.1 There are no randomised controlled trials which have evaluated the efficacy of using BDM to screen menopausal women and prevent fractures.**

Ideally, there should be data available from controlled trials where menopausal women are randomised to a screening programme or no screening programme and subsequently followed for 20-30 years (at the age when most fractures occur) to determine the effect on the number of individuals in whom fractures are prevented. No data studies with designs corresponding to Levels I-V (Table 1) are currently available.

**2.2 There is FAIR evidence that BDM can predict the risk of fracture in menopausal women. However, because of the considerable overlap between the distribution of bone mineral density for individuals who have and do not have fractures, BDM cannot reliably distinguish those who will have a fracture from those who will not.**

A recent meta analysis of prospective cohort studies (Level VI), shows that there is an inverse association between bone density and the risk of future fractures. The relative risk for a decrease in bone density of 1 SD below the age adjusted mean for all types of fractures at all sites was 1.5.

Most of the studies have short follow up and the extent to which the results can be extrapolated to the prediction of fractures in individuals which will occur in 20 to 30 years in the future is not known. The ability of BDM to predict fracture risk will not be the same for all age groups because of the increased importance of other risk factors with increasing age.

On the basis of data from case - control studies (Level VII) of hip fracture, BDM does not accurately distinguish between patients with recent (non-traumatic) fractures and those without fractures.

**2.3 Low bone density is only one of a number of risk factors for fracture in menopausal women, some of which have similar estimates for risk association with fractures.**

Scientific evidence of similar strength (Level VI) exists regarding many other risk factors in menopausal women that have similar independent predictive ability for fracture to that of bone mineral density. These include a history of maternal hip fracture, previous fractures of any type after the age of 50, self-rated health as fair to poor, previous hyperthyroidism, inability to rise from a chair without using one's arms, a faster resting pulse rate, and poorer depth perception.

**2.4 There appears to be no consensus about the appropriate applications of BDM between organisations that had published a report on this topic.**

A survey (Level VIII) of reports on the applications of BDM technologies suggests that there is wide variation in the views taken on the appropriate use of BDM for clinical and screening purposes. Studies based on more systematic review methods tended to be more conservative in their conclusions about the potential uses of BDM.

## 3. Effect of HRT in preventing fractures and preserving bone mass (3)

**3.1 There is FAIR evidence that ever-use of HRT is associated with a decrease in fractures of all types.**

Data from one small RCT (Level III) show a reduction in new vertebral fractures with HRT used for secondary prevention. However, the number of individuals who experienced a new vertebral fracture was reduced by a smaller amount (37%) and was not statistically significant.

For all other types of fracture, data are available only from cohort and case - control studies (Levels VI and VII). Pooled estimates from these observational studies show a tendency to a modest reduction in relative risk for hip fracture with ever use of HRT.

**3.2 There is FAIR evidence that current long-term use of HRT has a protective effect for fractures.**

Data from cohort and case – control studies (Levels VI and VII) comparing long term and short term users show a trend towards risk reduction for fractures with long term use of HRT. However, results from some studies did not reach statistical significance.

**3.3 There is FAIR evidence that there is no decrease in risk for hip fracture at older ages with ever use of HRT.**

Data from cohort and case – control studies (Levels VI and VII)) showed a decrease in the potential protective effect for hip fracture with age. At older ages, when most hip fractures occur, there was no statistically significant difference in fracture risk between ever and never users of HRT (Table 3).

**3.4 There is FAIR evidence that the longer the period since cessation of therapy, the smaller the protective effect of HRT on risk of hip fracture.**

Pooling the results from two cohort studies (Level VI) gives an estimated protective effect on hip fracture between former and never users of RR=0.88 when 2-14 years have elapsed since last estrogen use. After more than 15 years since estrogen treatment there was no evidence of benefit (RR=1.07).

**3.5 There is GOOD evidence that HRT, used alone or in combination with progestogens and / or calcium, for primary and secondary prevention, has a protective effect against bone mass loss, as measured by various BDM techniques at the forearm, spine and hip.**

A meta analysis of RCTs (Level I) showed a trend towards a positive effect of HRT on bone mass both in primary and secondary prevention. Effect sizes in the forearm and spine in studies of secondary prevention were larger than in studies of primary prevention and had wider confidence intervals.

**3.6 The effect of HRT in reducing bone loss has mainly been studied in women shortly after menopause. However, there is GOOD evidence that age does not attenuate the short term response to treatment.**

When the results of 43 RCTs examining skeletal response in women of various ages are examined, the protective effect of HRT appears to be the same for women who are under 60 years and those who are over 60 years old.

**3.7 There is FAIR evidence that the protective effect of HRT on the loss of bone mass may decline over time when therapy is started soon after the menopause, and that the protective effect wears off after cessation of treatment.**

Data from RCTs, case - control studies and case series (Levels III, VII and VIII) indicate that the protective effect of HRT on bone loss is only maintained when currently used. The protective effect appears to disappear progressively after cessation of therapy, reaching a rate of bone loss equal to that in untreated or placebo treated women (2-3% per year) within a few years after withdrawal of treatment. This point is critically important since therapy with HRT is generally prescribed around or soon after

the menopause and generally not for more than ten years, consequently leaving a period of 15-20 years between the cessation of treatment and the time when most fractures occur (> 75 years of age).

**3.8 Long term compliance with HRT is likely to be less than 50% for menopausal women.**

Data from different surveys (Level VIII) suggest that long term compliance with HRT is low (approximately 30%). This is mainly because of the presence of various side effects (e.g. breast tenderness, bleeding, depression), fear of cancer, dislike of taking tablets and failure to continue treatment when climacteric symptoms disappear. This is an important factor to take into account when considering the effectiveness of HRT, given the findings of reduced protective effect of HRT after cessation of therapy.

**4. Effect of intranasal salmon calcitonin in preventing fractures and preserving bone mass**

**4.1 There is FAIR evidence to support the efficacy of intranasal salmon calcitonin in decreasing the risk of fractures.**

Data from RCTs and case – control studies (Levels I, II, III and IV) provide mixed results about the protective effect of SCT(N) on the risk of fractures. However, a recent meta analysis of RCTs (Level I) concluded that the anti-fracture efficacy of calcitonin still remains to be established.**4.2 There is GOOD evidence demonstrating the short term efficacy of intranasal salmon calcitonin (SCT(N)) in preserving bone mass in both primary and secondary prevention in postmenopausal women.**

Several RCTs have shown that SCT(N) decreases bone loss and/or preserves bone mass in postmenopausal women. This is the case in both primary and secondary prevention, after both natural and surgical menopause.

**4.3 There is FAIR evidence demonstrating the long term preservation (5 year) of bone mass using SCT(N), but no data are available about the long term effect when treatment is started early after menopause.**

One RCT (Level III ) in primary prevention with a duration of five years shows a statistically significant increase in vertebral bone mass after 42 months of treatment compared with those women not treated, but not at the end of the five years.

**4.4 There are no prospective studies comparing the efficacy or the effectiveness of HRT andintranasal calcitonin.**

**Discussion**

Using the classification system for evidence outlined in Table 1, there is:

- FAIR evidence from prospective cohort studies suggesting that BDM can assess the risk of future fracture occurrence in populations over the short term, but not with a high degree of accuracy;
- FAIR evidence, from low quality RCTs and observational studies, showing the efficacy of HRT and SCT(N) in preventing fractures during therapy;
- GOOD evidence demonstrating the efficacy of HRT and SCT(N) in preserving bone mass during therapy;
- FAIR evidence that the effect of HRT diminishes and may eventually wear off after cessation of therapy.

Common limitations of the studies that have been undertaken are that sample sizes are small and follow up periods too short. Because many of these summaries of the evidence are based only on observational studies, it is not certain that they reflect a causal relationship. In addition, these studies are subject to various errors and biases.

Due to the relatively short follow up of the available studies, it is not possible to assess the ability of BDM to predict fractures which occur many years after measurement. Similarly, the long term positive and negative effects of HRT and SCT(N) are not known.

There is particular interest in the potential use of BDM for population screening programmes and in opportunistic screening for women around the menopause who seek advice from medical practitioners. Current evidence is insufficient to provide firm conclusions about the value of BDM screening. However, if it possible to get some indication of its potential effectiveness in preventing hip fractures.

Table 4 presents a number of scenarios, using realistic assumptions, for a BDM screening program linked to treatment with HRT in a hypothetical cohort of 20,000 menopausal women. For the scenario with 50% screening uptake, 30% long term compliance with treatment and 30% reduction in life-time fracture risk with HRT, one hip fracture would be avoided for every nine women identified through screening as being at risk, and who comply with therapy for 30 years. This apparently promising estimate represents the optimum benefit achievable, and has to be put in the context of the overall screening process.

Of the 20,000 women invited for screening, 10,000 are likely at attend for BDM. Of these, 1,600 will be identified as having a bone density of less than one SD below the population mean (assuming a Gaussian distribution) and will be offered HRT. Of those offered HRT, 576 will have been correctly identified (true positives) and 0173 (30%) of them will comply with therapy, so preventing 52 fractures. There will, however, also be 1,024 false positives, so that almost two thirds of women advised to take HRT would be unnecessarily having this treatment since they would not have had a fracture, under the assumptions used here.

Furthermore, under this scenario, of 10,000 women who present for screening, 948 who will go on to have a hip fracture will be advised that they are not at high risk (false negatives). Nearly two thirds of those who will sustain a fracture and who have a BDM will, therefore, have been falsely reassured.

When this broader perspective is considered, 393 women would need to be invited for screening and 197 actually attend in order to avoid one fracture. Thus, the overall impact of the program would be to reduce the number of fractures over the remaining lifetime of the cohort of 20,000 women from 3,050 to 2,998, that is, by 1.7%.

When all the scenarios presented in Table 4 are considered, a BDM screening program aimed at menopausal women might prevent between 1 and 7% of fractures. Taken together, these estimates of the effectiveness of such a program are not particularly encouraging from a public health perspective and are unlikely to represent good value for money.

For those formulating policy and considering offering such interventions to their patients, there are other potential effects to be considered. Current data suggest that use of HRT is associated with a 40-50% reduction in the risk of coronary heart disease among postmenopausal women and an increased risk of 30-70% for breast cancer, independent of levels of bone mass. A number of important social and ethical concerns must also be addressed and alternative approaches to preventing and treating osteoporosis require further consideration.

The currently available evidence does not support the use of BDM screening of menopausal women in combination with HRT or SCT(N) in the context of population or opportunistic screening for the prevention of fractions, and estimates based on what data are available are not encouraging about its potential effectiveness.

*Table 1 : Levels of scientific evidence*

| Level Highest (I) to Lowest (IX) | Strength of evidence | Type of study design | Conditions of scientific rigour* |
|---|---|---|---|
| I | Good | Meta-analysis of randomised controlled trials | Analysis of patient individual data<br>Meta-regression<br>Different techniques of analysis<br>Absence of heterogeneity<br>Quality of the studies |
| II | | Large sample randomised controlled trials | Assessment of statistical power<br>Multicentre<br>Quality of the study |
| III | Good | Small sample randomised controlled trials | Assessment of statistical power<br>Quality of the study |
| IV | to Fair | Non-randomised controlled prospective trials | Concurrent controls<br>Multicentre<br>Quality of the study |
| V | Fair | Non-randomised controlled retrospective trials | Historical controls<br>Quality of the study |
| VI | | Cohort studies | Concurrent controls<br>Multicentre<br>Quality of the study |
| VII | | Case-control studies | Multicentre studies<br>Quality of the study |
| VIII | Poor | Non-controlled clinical series<br>Descriptive studies: surveillance of disease, surveys, registers, data bases, prevalence studies | Multicentre |
| | | Expert committees, consensus conferences | |
| IX | | Anecdotes or case reports | |

* Quality of the study assessed by specific protocols and conditions of scientific rigour.

***Table 2 : Characteristics of common methods for measuring bone density***

| **Method** | **Accuracy** CV (%) | **Precision** CV (%) | **Time of scan** (minutes) |
|---|---|---|---|
| **SPA** Single Photon Absorptiometry | 2 - 8 | 2 - 5 | 5 - 15 |
| **DPA** Dual Photon Absorptiometry | 3-10 | 2 - 6 | 20 - 45 |
| **SXA** Single X-ray Absorptiometry | 5 | 1 | 10 -20 |
| **DXA** Dual X-ray Absorptiometry | 3-6 | 1 - 3 | 3 - 10 |
| **QCT** Quantitative Computed Tomography | 5 - 15 | 2 - 5 | 10 - 15 |
| **Ultrasound** | 20 | 2-4 | 5 |

CV = Coefficient of variation

***Table 3 : Relative risk of hip fracture according to age***

| Study | Age Group | | Relative Risk (95% CI) | |
|---|---|---|---|---|
| | Younger | Older | Younger | Older |
| Pagnini-Hill, 1991 | | avg age=73 | | 1.02 (0.81-1.27) |
| Naessén, 1990 | < 60 (trochanter)<br>< 60 (cervical hip) | > 60 (trochanter)<br>> 60 (cervical hip) | 0.37 (0.13-0.79)<br>0.58 (0.41-0.80) | 1.03 (0.74-1.40)<br>0.95 (0.75-1.18) |
| Kiel, 1987 | 65-74 | > 75 | 0.37 (0.05-2.46)[a] | 0.82 (0.21-3.24)[a] |
| Kanis, 1992 | < 80 | > 80 | 0.51 (0.31-0.84)[b] | 0.70 (0.29-1.66)[b] |
| Cauley, 1995 | < 75 | > 75 | 0.94 (0.52-1.69)[c] | 0.18 (0.04-0.77)[c] |

[a] = recent estrogen use (<= 2 years)
[b] = adjusted by age, previous fractures, body mass index
[c] = current users, multivariate-adjusted relative risk

***Table 4 : Potential impact of BDM screening and treatment with HRT in preventing hip fractures in a population of 20,000 menopausal women (under realistic assumptions)*** [a b c d e]

| Fracture Risk Reduction from HRT | Compliance = 30%<br>N hip fractures avoided<br>% hip fractures avoided<br>N needed to invite to screen per hip fracture avoided | Compliance = 50%<br># hip fractures avoided<br>% hip fractures avoided<br>N needed to invite to screen per hip fracture avoided |
|---|---|---|
| **Screening Uptake 50%:** N false negatives =948, N false positives=1024, N needed to offer HRT=1600 | | |
| 15%<br>(RR=0.85) | 27<br>0.9%<br>803 | 44<br>1.5%<br>474 |
| 30%<br>(RR=0.70) | 53<br>1.7%<br>393 | 87<br>2.9%<br>234 |
| 50%<br>(RR=0.50) | 87<br>2.9%<br>234 | 145<br>4.8%<br>140 |
| **Screening Uptake = 70%:** N false negatives=1327, N false positives=1434, N needed to offer HRT=2240 | | |
| 15%<br>(RR=0.85) | 38<br>1.2%<br>560 | 62<br>2.0%<br>334 |
| 30%<br>(RR=0.70) | 74<br>2.4%<br>278 | 122<br>4.0%<br>166 |
| 50%<br>(RR=0.50) | 122<br>4.0%<br>166 | 203<br>6.7%<br>100 |

These scenarios were calculated using the following assumptions:

- Assume a cohort of 20,000 menopausal women are invited to a BDM screening programme and those identified with a bone density < 1 SD below the healthy adult mean are treated with HRT.
- Bone density values follow a Gaussian distribution in the population
- The lifetime risk of hip fracture is 15.25% for women over 50 years [44]

[a] Hip fracture RR=2.6 for 1 SD decrease in BMD below age adjusted mean
[b] For those who comply, compliance continues for their remaining lifetimes (about 30 years)
[c] There is no decrease in the protective effect of HRT over time
[d] No side effects are taken into account
[e] The reduced beneficial effect on those who would be treated because some women would already be taking HRT for other reasons is not taken into account.

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3. Sampietro-Colom L, Rico R, Granados A, Asua J. Background Paper Three. A review of the evidence of hormone replacement therapy and calcitonin in reducing bone loss and fractures. Barcelona, Spain, September, 1996.