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WELCOME LETTER

There is ample evidence that bone mineral density (BMD) screening effectively identifies women and men who can benefit from treatment for osteoporosis, so reducing the risk of fractures and spinal abnormalities. Hopefully, the recent call by the US Preventive Services Task Force for routine screening for women aged 65 and older will help promote the local Australian lobby on osteoporosis initiatives. Among other things on the lobbyists' agenda are a wider availability of Medicare Benefits Schedule rebates on bone densitometry items and drugs under the Pharmaceutical Benefits Scheme.

On page 9, we review the US Task Force recommendations on screening. While bone densitometry is well established, the choice of technique, interpretation of results, the optimal frequency of testing and treatment decisions is all subject to debate.

In a ***Local Commentary*** on page 8, we present a contribution by Adelaide endocrinologists George Phillipov and Patrick Phillips on dual-energy X-ray absorptiometry (DEXA) versus quantitative ultrasound (QUS). A noteworthy point they raise is that the portability of QUS lends itself to a wider assessment of osteoporosis across the general community, particularly in remote and rural areas.

Our other major review (page 4) looks at a recently published meta-analysis of treatments for osteoporosis. The authors note that while evidence is crucial in clinical decision-making, the relative weight a physician might place on weaker and stronger evidence, as well as their own or their patient's values or preferences are also factors to be taken into account during treatment. For example, a patient whose treatment is covered by Medicare may have different preferences to a patient with private health insurance.

Also of relevance to any discussion about osteoporosis is whether patients with osteoporotic fractures are adequately investigated and followed up. An abstract on this topic appears in ***Conference Highlights*** from the recent 24th meeting of the American Society for Bone and Mineral Research. The study tracked the somewhat lackadaisical performance of 14 orthopaedic surgeons from Salt Lake City, Utah, in achieving subsequent osteoporotic medical treatment for patients despite remuneration for participating in the research.

We hope you find this issue useful and, as always, welcome any comments or suggestions.

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2nd International Conference on "Osteoporosis in Men"

2-5 April, 2003
Genoa, Italy

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AOA Continuing Orthopaedic Education Meeting - 'Arthroscopy'

4-6 April, 2003
Perth, Australia

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Spine Society of Australia Annual Meeting

25-27 April, 2003
Canberra, Australia

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Annual Scientific Meeting of the Australian Rheumatology Association

18-21 May, 2003
Sydney, Australia

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International Conference on Metabolic Bone Disease 2003: A Combined Meeting of the ANZBMS and International Bone and Mineral Society

10-13 June, 2003
Sunshine Coast, Australia

Contact: ANZBMS, 145 Macquarie Street, Sydney NSW 2000, Australia
Tel: (02) 9256-5405
Fax: (02) 9241-4083
E-mail: anzbms@racp.edu.au

EULAR 2003: European Congress of Rheumatology

18-21 June, 2003
Lisbon, Portugal

Contact: EULAR Secretariat, Witikonerstrasse 15, CH-8032 Zurich, Switzerland.
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Brain study of back pain sufferers yields intriguing results

Patients with lower back pain that cannot be traced to a specific physical cause may have abnormal pain-processing pathways in their brains, according to a new study led by University of Michigan researchers.

The effect, which as yet has no explanation, is similar to an altered pain perception effect in fibromyalgia patients recently reported by the same research team.

In fact, the study finds, people with lower back pain say they feel severe pain, and have measurable pain signals in their brains, from a gentle finger squeeze that barely feels unpleasant to people without lower back pain. People with fibromyalgia felt a similar level of pain from a squeeze of the same intensity.

But the squeeze's force must be increased sharply to cause healthy people to feel the same level of pain — and their pain signals register pain in different brain areas.

To correlate subjective pain sensation with objective views of brain signals, the researchers used functional magnetic resonance image (fMRI) scanning. They looked at the brains of 15 people with lower back pain whose body scans showed no mechanical cause, such as a ruptured disk, for their pain. They also looked at 15 fibromyalgia patients and 15 normal control subjects.

"The fMRI technology gave us a unique opportunity to look at the neurobiology underlying tenderness, which is a hallmark of both lower back pain and fibromyalgia," said researcher Dr Daniel Clauw. "These results, combined with other work done by our group and others, have convinced us that some pathologic process is making these patients more sensitive. For some reason, still unknown, there's a neurobiological amplification of their pain signals."

Postmenopausal glucocorticoid users more likely to fracture

Daily dosing with oral glucocorticoids (corticosteroids) for chronic diseases was found to be a strong predictor of spinal fracture at one year, according to new data presented at the annual scientific meeting of the American College of Rheumatology (ACR) late last year. The risk of fracture was found to increase incrementally with every 1 mg increase above 7.5 mg in the daily dose of the glucocorticoid.

"Osteoporotic fractures are typically associated with postmenopausal osteoporosis, but up to one-half of patients on chronic glucocorticoid therapy may experience an osteoporotic fracture," said Dr Tjeerd van Staa, Department of Pharmacoepidemiology and Pharmacotherapy, University of Utrecht, the Netherlands.

At one year, postmenopausal women using glucocorticoids were almost six times more likely to experience spinal fractures when compared to a group of postmenopausal women with low bone mineral density (BMD) who did not use glucocorticoids. This increased fracture risk is notable since the glucocorticoid patients were younger, had higher baseline BMD scores, and fewer pre-existing spinal fractures.

Bone mineral density testing could save millions

Data presented at the annual scientific meeting of the American College of Rheumatology last year estimated that a modest 10% increase in bone mineral density (BMD) testing to detect osteoporosis could save the US Medicare system US$15.5 million over three years. Projected medical cost savings of US$32.3 million would offset the extra cost of testing.

It is estimated that in 2001 only 12% (or 1.8 million of 14.9 million) of women aged 65 and older with osteoporosis or osteopenia (low bone mass) received a Medicare-reimbursed BMD test to detect the disease. The study projects that testing 180,000 (or just 10%) additional women with osteoporosis or osteopenia would reduce the incidence of osteoporotic fractures at the hip, spine and wrist by more than 6500 over three years and result in net Medicare savings.

"The vast majority of the women over age 65 at risk of osteoporotic fracture remain undiagnosed and untreated," said Dr Kenneth Saag, Department of Medicine, Division of Rheumatology and Clinical Immunology, the University of Alabama at Birmingham.

Delays in diagnosis for ankylosing spondylitis patients

Although a majority (61%) of respondents with ankylosing spondylitis (AS) experience symptoms of AS by age 29, most have a delayed diagnosis, with many seeing multiple doctors in the process, according to a national survey of more than 2000 AS patients commissioned by the Spondylitis Association of America (SAA).

More than half (54%) were not diagnosed with AS until at least five years after their symptoms first appeared and three out of ten (30%) endured symptoms for more than 10 years before they were diagnosed, the survey found. Almost one quarter (24%) of those surveyed saw five or more health professionals in pursuit of a diagnosis.

US Preventive Services Task Force recommends routine osteoporosis screening

The US Preventive Services Task Force has recommended that women aged 65 and older be routinely screened for osteoporosis to reduce the risk of fracture and spinal abnormalities often associated with the disease. The Task Force also recommended that routine screening begin at age 60 for those women identified as high risk because of their weight or estrogen use.

The Task Force is an independent panel of experts sponsored by the Agency for Healthcare Research and Quality (AHRQ). The recommendations, which were published in the September 2002 issue of the *Annals of Internal Medicine*, and summarised on page 9 of this issue of the *Australasian Journal of Bone and Joint Medicine*, mark the first time the Task Force has called for routine osteoporosis screening.

For women who live to be 85, approximately 50% will have an osteoporosis-related fracture during their lives; 25% of these women will develop an abnormality of the spine; and 15% will fracture their hip. While no clinical studies have been done to assess the effectiveness of screening in reducing osteoporotic fractures, there is ample evidence that bone density testing can adequately identify women who could benefit from treatment.

Bisphosphonates have proved effective at reducing the risk of fracture in women with low bone density, leading the Task Force to believe that screening can be beneficial.

"The evidence shows that the risk for osteoporosis and fractures increases with age, and the means are now available to detect low bone density and treat it," said evidence reviewer Dr Heidi Nelson, of the Evidence-based Practice Center at Oregon Health & Science University.

One variable for physicians to consider is that several technologies are available to measure bone density. Dual-energy X-ray absorptiometry, known as DEXA, is considered the most extensively validated test against fracture outcomes. Published studies consistently show that the probability of receiving a diagnosis of osteoporosis depends on the choice of technology and site of the test (forearm, hip, heel, etc.). The optimal frequency of testing is unclear, but intervals of two to five years are most consistent with current understanding of the tests.

The benefits of screening large segments of the population for osteoporosis are tempered by harms of testing. Potential harms may arise from inaccuracies and misinterpretations of bone density tests. False positives could lead to inappropriate treatment and false negatives could lead to missed treatment opportunities. Costs of tests and treatment are also factors to consider when screening.

The US Preventive Services Task Force, the leading independent panel of private-sector experts in prevention and primary care, conducts rigorous, impartial assessments of all the scientific evidence for a broad range of preventive services. Its recommendations are considered the gold standard for clinical preventive services.

- **For a more comprehensive review of the US Preventive Services Task Force recommendations on osteoporosis screening, see page 9 of this issue of the *Australasian Journal of Bone and Joint Medicine*.**

No difference between ionised bracelet and placebo

Mayo Clinic researchers report wearing ionised bracelets for the treatment of muscle and joint pain is no more effective than wearing placebo bracelets.

Authors of the study, published in the *Mayo Clinic Proceedings*, randomly assigned 305 participants to wear an ionised bracelet for 28 days and another 305 participants to wear a placebo bracelet for the same duration.

The study volunteers were men and women 18 and older who had self-reported musculoskeletal pain at the beginning of the study. Neither the researchers nor the participants knew which volunteers wore an ionised bracelet and which wore a placebo bracelet. Bracelets were worn according to the manufacturer's recommendations.

Both groups reported significant improvement in pain. However, researchers found no difference in the amount of self-reported pain relief between the two groups. The study authors conclude that the equivalent, subjective improvement in pain scores calls into question the true benefit of using an ionised bracelet.

Principal investigator Dr Robert Bratton says the study is important because so many patients are interested in alternative medicine. "We need to look at what our patients are doing for their various problems," he says, "and undertake objective, controlled studies to prove whether or not these treatments are beneficial."

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Assessing the impact of therapies for postmenopausal osteoporosis

Cranney and colleagues recently published a review[1] of a series of meta-analyses[2] that they have performed on various osteoporosis therapies. The series, published in the journal *Endocrine Reviews*, looked at the effects of the bisphosphonates (alendronate and risedronate), calcium alone and in combination with vitamin D, as well as hormone replacement therapy (HRT), raloxifene and calcitonin. The review and meta-analyses found that only the bisphosphonates (alendronate and risedronate) reduced the risk of both nonvertebral and vertebral fractures. Therapies that reduced vertebral fracture included raloxifene, etidronate, vitamin D, and calcitonin.

According to Cranney and colleagues, the aim of the systematic review was to provide "the best current estimates of the magnitude of the effects they may expect with current therapies for osteoporosis".[2] They believe that the reviews, in conjunction with considerations such as toxicity and cost, will assist physicians in formulating treatment policies.[2]

Methodology

The authors of the meta-analyses undertook wide-ranging searches, only including trials that had explicit eligibilty criteria and were randomised. Each trial was evaluated on facets which could have had an impact on validity: adequate concealment of randomisation, blinding, and whether investigators included all patients in the groups to which they were randomised (intention-to-treat analysis), as well as the completeness of follow-up, in which the direction of bias varies across studies.[1,2] Two reviewers also made independent, reproducible decisions regarding study inclusion and assessments of study validity for each of the meta-analyses.[1]

The authors note that, with respect to blinding, concealed allocation and follow-up, the validity of the alendronate trials proved the most robust.[1]

Comparing treatment effects

Cranney *et al*[1] presented several summary tables that juxtaposed the impact of osteoporotic treatment on vertebral and nonvertebral fractures and bone density (**Tables 1, 2** and **3**). However, they caution that readers should be wary of making too strong a deduction from the between-trial comparisons, and that dependable conclusions about the relative effectiveness of osteoporotic therapies require head-to-head comparisons. Study populations may vary in their responsiveness to treatment because of differences in bone density, prevalent fractures, postmenopausal status, co-interventions, and comorbidity.

Results of vertebral fractures

The authors report that there was a significant reduction in the pooled relative risk for vertebral fractures with alendronate, etidronate, risedronate, raloxifene, calcitonin and Vitamin D. While calcium, fluoride and HRT showed trends toward reduction in vertebral fractures, the confidence intervals (CIs) had overlapped 1.0, showing the data had not excluded a null or detrimental effect with these therapies and therefore the results were not statically significant.

They add that a sparseness of data made it hard to adequately assess the effect of dose on vertebral fractures with many of the therapies. With alendronate, there was sufficient data to conclude the treatment effect was similar across doses.

Results of nonvertebral fractures

They conclude that the only two therapies which had a significant pooled treatment effect on nonvertebral fracture reduction were alendronate 10–40 mg (RR, 0.51; 95% CI, 0.38–0.69; $p < 0.01$) and risedronate (5 mg) (RR, 0.73; 95% CI 0.61–0.87; $p < 0.01$) (**Table 2**). They note the

Table 1. Magnitude of effect on vertebral fractures

Intervention	No. of trials/patients	Relative risk (95% CI)	Relative risk p value	Heterogeneity p value
Calcium	5 (576)	0.77 (0.54–1.09)	0.14	0.40
Vitamin D	8 (1130)	0.63 (0.45–0.88)	< 0.01	0.16
Alendronate (5–40 mg)	8 (9360)	0.52 (0.43–0.65)	< 0.01	0.99
Etidronate (400 mg)	9 (1076)	0.63 (0.44–0.92)	0.02	0.87
Risedronate	5 (2604)	0.64 (0.54-0.77)	0.01	0.89
Calcitonin*	1 (1108)	0.79 (0.62-1.00)	0.05	n/a
Raloxifene	1 (6828)	0.60 (0.50-0.70)	0.01	n/a
HRT	5 (3117)	0.66 (0.41, 1.07)	0.12	0.86
Fluoride (4 yr)	5 (646)	0.67 (0.38, 1.19)	0.17	0.01

* Due to the potential for publication bias, the estimate for the larger RCT estimate from the PROOF trial is presented. The pooled estimate for calcitonin from the PROOF trial and the three smaller studies combined is 0.46 (95% CI 0.25-0.87, p = 0.02, n = 1404).

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Table 2. Magnitude of effect on nonvertebral fractures

Intervention	No of trials/patients	Relative risk (95% CI)	Relative risk p value	Heterogeneity p value
Calcium	2 (222)	0.86 (0.43, 1.72)	0.66	0.54
Vitamin D	6 (6187)	0.77 (0.57, 1.04)	0.09	0.09
Etidronate	7 (867)	0.99 (0.69, 1.42)	0.97	0.94
Alendronate (5 mg)	8 (8603)	0.87 (0.73, 1.02)	0.09	0.31
Alendronate (10–40 mg)	6 (3723)	0.51 (0.38, 0.69)	< 0.01	0.88
Raloxifene	2 (6961)	0.91 (0.79, 1.06)	0.24	0.43
Calcitonin*	1 (1245)	0.80 (0.59, 1.09)	0.16	n/a
Risedronate	7 (12,958)	0.73 (0.61, 0.87)	< 0.01	0.81
HRT	6 (3986)	0.87 (0.71, 1.08)	0.10	0.57
Fluoride	5 (950)	1.46 (0.92, 2.32)	0.11	0.06

* Due to the potential for publication bias, estimate for the larger RCT estimate from the PROOF trial is presented. The pooled estimate for calcitonin from the PROOF trial and the three smaller studies combined is 0.52 (95% CI 0.22–1.23, p = 0.14, n = 1481).

study designs in trials of the two agents were strong, and results were consistent from study to study. Two alendronate trials achieved loss to follow-up of less than 5%.

There were larger treatment effects on nonvertebral fractures with larger doses of alendronate with a pooled relative risk of 0.51 in the 10- to 40-mg dose and 0.87 in the 5-mg trials. For alendronate only, the authors had data on fracture sites in a sufficient number of patients to calculate the relative effect on the occurrence of osteoporotic versus non-osteoporotic fractures. Osteoporotic fractures were defined by an association between low calcaneal bone density and the particular category of fracture. Osteoporotic fracture sites included forearm, hip, rib, leg, patella, pelvis, and hands versus all fractures in which the relative risk was less than 1.5. The pooled relative risk was 0.46 for osteoporotic and 0.57 for the non-osteoporotic fractures with alendronate 10–40 mg. Channey *et al* also note that the relative risk reductions were larger with alendronate 10–40 mg in comparison to the 5-mg dose.

They add the treatment effects were very similar with alendronate across all fracture types, and so were thus very similar for hip fractures versus other nonvertebral fractures. They conclude that the consistent effect of alendronate on both osteoporotic and non-osteoporotic fractures supported applying the pooled relative risk estimate of 0.51 and the associated CIs to all types of nonvertebral fractures. They comment "based on our analyses, the inference that pooled nonvertebral fracture reduction relative risks apply to all such fractures is stronger for alendronate than other treatments."

Results for bone density

Alendronate 10–40 mg and HRT displayed the largest treatment effects on the lumbar spine, with intermediate effects observed with risedronate and etidronate. Alendronate, raloxifene, calcium, risedronate, and HRT all demonstrated convincing, relatively large effects on bone density sites (hip, femoral neck, forearm, and total body bone density) in comparison to controls. The authors also found the impact of treatment on bone density was similar in the prevention and the treatment populations with most of the medications. Higher doses of risedronate, alendronate and HRT had a greater impact on bone density, while longer treatment durations with alendronate, risedronate, raloxifene and HRT resulted in larger treatment effects on lumbar spine bone density.

They explain that in their a priori hypotheses, they had suggested the extent of the treatment effects might vary if therapies were used concurrently with calcium or vitamin D. This proved the case in lumbar spine and total bone density with calcium 500 mg and vitamin D used concurrently, as it did with alendronate and calcium.

Implications for management of osteoporosis

According to the authors, while evidence is crucial in clinical decision-making, other facets also play in a part in treatment decisions. Some of the factors that might inform any decision would include the relative weight a physician might place on weaker and stronger evidence, as well as their own or their patient's values or preferences. For example, a patient whose treatment is covered by Medicare may have different treatment preferences to a patient with private health insurance.

They raise some issues decision-makers could ponder. In summarising the evidence from their reviews, they suggest vitamin D (hydroxylated), calcitonin, raloxifene, and the bisphosphonates – etidronate, risedronate, and alendronate – all reduce vertebral fractures. However, based on the methodological quality of the studies, treatment magnitude, narrowness of the confidence intervals, and the consistency of the results from study to study, they conclude the inferences are strongest for alendronate and risedronate. In terms of HRT, they suggest it will ultimately prove to have a large beneficial impact on vertebral fracture incidence.

They point out that their meta-analyses found only alendronate and risedronate provided convincing evidence for nonvertebral fracture reduction. They found the trials they reviewed indicated that etidronate and raloxifene probably have only small, if any, effects on nonvertebral

fracture while the sparse data for calcium and calcitonin provided little information. And, while an appreciable trend suggests that HRT will reduce nonvertebral fracture, the confidence interval overlaps the point of no effect. They recommend continued caution in making any assumptions about the effect of HRT on nonvertebral fractures.

In exploring the relationship between bone density and fracture through a regression analysis using data from these meta-analyses, they found BMD was useful in predicting the impact of therapies on vertebral but not nonvertebral fractures.

In terms of the magnitude of the treatment effect, they note that relative risk reductions are of the order of one half for alendronate, both for vertebral and nonvertebral fractures. For risedronate, the relative risk reductions are slightly more than one third for vertebral fractures, and one quarter for nonvertebral fractures. At the same time they caution that decision makers should be wary of making inferences from indirect, rather than head-to-head, comparisons of drugs.

Another issue raised by the authors is that of absolute risk. They point out that patients whose absolute risk is low can expect small absolute benefits from treatment. Those patients at higher risk can anticipate much greater absolute benefits, and may be willing to tolerate more in the way of inconvenience, costs, or medication-induced side effects. When making recommendations to patients, clinicians may want to take into account the number of patients one must treat (NNT) to prevent a vertebral or nonvertebral fracture (**Table 3**).

Summary of conclusions

In moving towards a summary of their conclusions, Cranney *et al* state that many factors weigh in the final treatment decisions. These include the strength of the evidence, additional benefits, risks, adverse effects, and the price of different medications.

In assessing the magnitude of effect of the various medications covered in their meta-analysis, they point out that the bisphosphonates alendronate and risedronate have strong evidence of their efficacy in relation to vertebral or nonvertebral fractures. Treatment options such as HRT, vitamin D, or calcitonin do not meet as stringent criteria.

"Those who would choose a treatment with proven impact, and who also feel that nonvertebral fracture is the most important outcome, will have little difficulty choosing alendronate or risedronate," the authors comment.

In terms of continued uncertainties about the treatment of osteoporosis they highlight the impact of HRT, the relative impact of different therapies, the optimal duration of therapy with antiresorptive agents, and health-related quality of life rate as the most important unanswered questions.

However, they conclude that "our systematic reviews have clarified what we know, and what remains in question." "Those responsible for recommending management strategies for osteoporosis should take full advantage of our data."

Practice points

- Evidence is crucial in the final treatment decision
- Other factors include risks and benefits, the price of different medications, and the treatment preference of the patient
- Only alendronate and risedronate reduced the risk of both vertebral and non-vertebral fracture
- The relative risk reduction for vertebral and nonvertebral fractures with alendronate 10–40 mg was approximately 49%. For risedronate, the relative risk reduction was approximately 36% for vertebral fractures, and 27% for nonvertebral fractures.

References

1. Summary of Meta-Analyses of Therapies for Postmenopausal Osteoporosis. A Cranney, G Guyatt, L Griffin *et al. Endocrine Reviews* 2002; **23**: 570-578.
2. Meta-Analyses of Therapies for Postmenopausal Osteoporosis. The Osteoporosis Methodology Group and the Osteoporosis Research Advisory Group. *Endocrine Reviews* 2002; **23**: 496-507.

B&J Editorial

Table 3. NNT to prevent a vertebral and nonvertebral fracture over a period of 2 years

Drug	Vertebral fracture		Nonvertebral fracture
	NNT (95% CI) over 2 yr for low-risk population† (risk untreated 0.12%)	NNT (95% CI) over 2yr for high risk population (risk untreated 2.88%)	NNT to prevent one fracture (95% CI) for high-risk population (risk untreated 8.65%)
Vitamin D	2252 (1515, 6944)	94 (63, 289)	Effectiveness not established
Alendronate	1790 (1507, 2455)	72 (61, 99)	24 (19, 37)
Etidronate	2252 (1042, 1488)	94 (62, 434)	Effectiveness not established
Risedronate	2315 (1812, 3623)	96 (75, 151)	43 (30, 89)
Raloxifene	2381 (1894, 3472)	99 (79, 145)	Effectiveness not estabished

†Low-risk population defined by BMD.

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A pilot randomized trial comparing CD34-selected versus unmanipulated hemopoietic stem cell transplantation for severe, refractory rheumatoid arthritis

J Moore, P Brooks, S Milliken *et al*
Arthritis and Rheumatism 2002; **46**: 2301-2309

Objective
Evidence from animal studies, case reports, and phase I studies suggests that hemopoietic stem cell transplantation (HSCT) can be effective in the treatment of rheumatoid arthritis (RA). It is unclear, however, if depletion of T cells in the stem cell product infused after high-dose chemotherapy is beneficial in prolonging responses by reducing the number of infused autoreactive T cells.

This pilot multicenter, randomized trial was undertaken to obtain feasibility data on whether CD34 selection (as a form of T cell depletion) of an autologous stem cell graft is of benefit in the HSCT procedure in patients with severe, refractory RA.

Methods
Thirty-three patients with severe RA who had been treated unsuccessfully with methotrexate and at least one other disease-modifying agent were enrolled in the trial. The patients received high-dose immunosuppressive treatment with 200 mg/kg cyclophosphamide followed by an infusion of autologous stem cells that were CD34 selected or unmanipulated. Safety, efficacy (based on American College of Rheumatology [ACR] response criteria), and time to recurrence of disease were assessed on a monthly basis for up to 12 months.

Results
All patients were living at the end of the study, with no major unexpected toxicities.

Overall, on an intent-to-treat basis, ACR 20% response (ACR20) was achieved in 70% of the patients. An ACR70 response was attained in 27.7% of the 18 patients who had received CD34-selected cells and 53.3% of the 15 who had received unmanipulated cells ($p = 0.20$). The median time to disease recurrence was 147 days in the CD34-selected cell group and 201 days in the unmanipulated cell group ($p = 0.28$). There was no relationship between CD4 lymphopenia and response, but 72% of rheumatoid factor (RF)-positive patients had an increase in RF titer prior to recurrence of disease.

Conclusion
HSCT can be performed safely in patients with RA, and initial results indicate significant responses in patients with severe, treatment-resistant disease. Similar outcomes were observed in patients undergoing HSCT with unmanipulated cells and those receiving CD34-selected cells. Larger studies are needed to confirm these findings.

Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) osteoarthritis hand index

N Bellamy, J Campbell, B Haraoui *et al*
Osteoarthritis and Cartilage 2002; **10**: 855-862

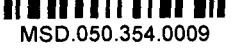
Objective
To develop a reliable, valid, and responsive self-administered questionnaire to probe pain, stiffness and physical disability in patients with osteoarthritis (OA) of the hand.

Design
In order to assess the dimensionality of the symptomatology of hand OA, a self-administered questionnaire was developed to probe various aspects of pain (10 items), stiffness (two items), and physical function (83 items). The question inventory was generated from eight existing health status measures and an interactive process involving four rheumatologists, two physiotherapists, and an orthopaedic surgeon.

Results
Face-to-face interviews were conducted with 50 OA hand patients; 39 females and 11 males with mean age 62.8 years and mean disease duration 9.4 years. Items retained were those which fulfilled specified selection criteria: prevalence 60% and mean importance score approximating or exceeding 2.0. Item exclusion criteria included low prevalence, gender-based, ambiguous, duplicates or similarities, alternatives, composite items, and items that were too restrictive.

This process resulted in five pain, one stiffness and nine function items which have been proposed for incorporation in the AUSCAN Index.

Conclusions
Using a traditional development strategy, we have constructed a self-administered multi-dimensional outcome measure for assessing hand OA. The next stage includes reliability, validity and responsiveness testing of the 15-item questionnaire.



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Limited resources exist to meet the demand for osteoporosis assessment which is increasing as the population ages and public awareness increases.[1] In response to this demand, a new technology based on ultrasound has been introduced to assess bone status. This technology, known as quantitative ultrasound (QUS)[2], addresses several existing practical issues concerning portability, analysis times and general ease of use. At present dual-energy X-ray absorptiometry (DEXA) is the standard method for osteoporosis assessment and there is a Medicare rebate for the diagnosis and monitoring of osteoporosis, when specific criteria are met.[3] Although DEXA is often referred to as the 'gold standard' for measuring bone mineral density (BMD), the designation and implication is incorrect.[4] As no certified reference standard exists for absolute BMD quantitation, no method can qualify as a 'gold standard', but only as a 'consensus' or 'reference' method. DEXA therefore cannot provide an accurate determination of BMD, and is subject to specific intrinsic quantitation errors.[5,6] DEXA is also expensive, difficult to use and has limited portability. QUS has significant practical advantages when compared to DEXA, but its widespread application to assess fracture risk for people within the metropolitan and rural Australian communities is impeded by the lack of an appropriate Medicare rebate.

The recent report by Pocock *et al*,[7] discussing the potential role of QUS in the diagnosis and management of osteoporosis is both timely and relevant. Pocock *et al* examined the predictive ability of calcaneal QUS to identify femur and spinal osteoporosis as classified by DEXA. They concluded that they could not recommend QUS as an independent technique for osteoporosis investigations, but implied it had a potential role for "pre-screening". However, closer examination of Pocock *et al*'s findings, specifically Fig 2B, reveals that women with QUS values below the lower set threshold (≤70), comprise at least 98.5% of all women classified with DEXA-hip osteoporosis (false-negative rate of 1.5%). The stated 8% false negative rate occurs because QUS does not efficiently predict DEXA-spine osteoporosis (see Fig. 2A). This comparison, and the authors' inference, should be tempered by the fact that inter-site DEXA comparisons also have poor sensitivity – a diagnosis of DEXA-hip osteoporosis, will only correctly predict about 45% of all women with DEXA-spine osteoporosis[8] (false negative rate of 55%). Furthermore, a recent Australian study found that QUS was better than DEXA in defining women with multiple fractures.[9] Therefore heel-QUS and hip-DEXA measurements identify the same general "osteoporosis" population, and are equivalent in terms of predicting long-term hip fracture risk.[10] Since the primary goal of osteoporosis programs is to reduce the incidence of hip fracture, QUS has significant practical advantages over DEXA. Those advantages are recognised in other countries, like the US, where a rebate is available.

In conclusion, it is well established that QUS measurements relate directly to bone density and possibly to some aspects of trabecular architecture.[11] There is also evidence that QUS measurements are able to provide reliable estimates of fracture risk, and most importantly, for fracture risk at the hip. The portability, and other features of QUS, allow for a wider assessment of osteoporosis and fracture risk across the general community, and this approach should be encouraged and promoted, especially in remote and rural areas.

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Guidelines review: Screening for postmenopausal osteoporosis

Osteoporosis places a huge burden on Australian patients and their families and carers, as well as the healthcare system as a whole. The condition has been estimated to be more prevalent than high cholesterol, allergies or the common cold,[1] and is estimated to affect nearly two million Australians which, at the present rate, will increase to three million people by 2021.[1] The burden placed on the healthcare system and the economy in general is considerable with estimates of $1.9 billion dollars per annum in direct costs, and $5.6 billion in indirect costs, such as lost earnings, volunteer costs etc.[1]

However, in the light of these statistics, there is good news in that osteoporosis or its manifestations are treatable, if not preventable.[1] Numerous therapies are indicated for osteoporosis. Bisphosphonates (alendronate and risedronate), which are indicated first-line, have been shown to reduce the relative risk of spinal fracture as well as non-spinal fractures, including those of the hip.[2] Raloxifene, also first-line, has shown good efficacy in spinal fractures but has had less success in non-spinal fracture prevention.[2] Etidronate, a less potent bisphosphonate, and hormone replacement therapy, have both been shown to reduce the risk of spinal fractures, but there is less evidence for efficacy against non-spinal fractures. Other treatments such as calcitriol, dietary measures such as increased vitamin D, with or without calcium supplementation, have also been investigated.[2]

Given the disease burden and the availability of effective treatments, physicians are faced with the decision about whom to screen for osteoporosis. There is disagreement in the literature about this issue,[3] reflecting gaps in evidence such as the risk factors to use to identify appropriate women for screening.[3] A recently published review[3] from the US sort to clarify the topic, investigating issues such as the role of risk factors in identifying at-risk women, techniques to identify fracture risk, the effectiveness of treatments to reduce fracture risks and the harms of screening and treatment.[3]

Osteoporotic bones – the causes and effects

Osteoporosis has been defined as "a systematic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk."[3] Deterioration in BMD or bone microarchitecture may come about due to factors related to age, hormone, diet, lifestyle, genetic factors, disorders of the thyroid, liver, kidney or bowels, as well as some medications including some corticosteroids, anti-convulsants or contraceptives.[1]

Estimates put the risk of a postmenopausal woman suffering from an osteoporosis-related fracture at 50% over their lifetime.[3] This may be due to a non-vertebral fracture such as a hip fracture, which is associated with high mortality rates and considerable loss of independence. Other common fractures involve the vertebrae, which in some cases may cause severe pain.[3]

Design of the osteoporosis screening study

The *Screening for Postmenopausal Osteoporosis: A Review of the Evidence for the US Preventive Services Task Force* report[3] analysed data from previous studies of postmenopausal women and osteoporosis and addressed the effectiveness of risk factor assessment, bone density tests, or treatment. The data was extracted from relevant studies available through MEDLINE (1966 to May 2001), HealthSTAR (1975 to May 2001) and Cochrane databases. The study[3] did not identify any papers that addressed the question of the effectiveness of screening in reducing osteoporotic fractures. For this reason, the authors have based recommendations about screening on the evidence provided by risk factor assessments, bone density testing and how successful they are at identifying women who could ultimately benefit from treatment.[3]

Assessment of risk factors in women over 65 years

Several different studies have been undertaken to determine which risk factors are significant predictors of bone fracture. For the most part, these studies have varying definitions of risk factors, which makes a combined quantitative calculation of risk difficult. One comprehensive US study of 9516 white women ≥ 65 years identified 14 clinical risk factors that were significant predictors of osteoporotic hip fracture (Table 1).

Women with five or more of the risk factors had increased rates of hip fracture compared with women who had zero to two risk factors, at all levels of calcaneal bone density.

Assessment of risk factors in women under 65 years

Data[3-11] is shown in **Table 2** from eight observational studies of risk factors for fractures. The studies were conducted in populations in which at least 50% of the participants were less than 65 years of age.

Decision rules for selecting at-risk women

The screening study identified 10 cross-sectional studies that described methods of determining risk for low bone

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Table 1. Risk factors predicting hip fracture in osteoporotic women over 65 years of age

Age	Not walking for exercise
Maternal hip fracture	Lack of ambulation
No weight gain	Inability to rise from a chair
Height	Poor scores on two measures of vision
Poor self-rated health	High resting pulse
Hyperthyroidism	Any fracture since 50 years of age
Current use of benzodiazapines, anticonvulsants or caffeine	Decrease in calcaneal bone density

density for individual women based on selected clinical risk factors. For the most part the small numbers of non-representative patients meant that the studies lack generalisability and many are not validated. A comparison of clinical decision rules for bone density testing was undertaken in a Canadian trial.[12] Five decision rules were tested: Simple Calculated Osteoporosis Risk Estimation (SCORE); Osteoporosis Risk Assessment Instrument (ORAI); Age, Body Size, No Estrogen (ABONE); and body weight less than 70 kg (weight criterion); and the scale used in the National Osteoporosis Foundation (NOF) practice guidelines.[12] SCORE and ORAI were found to be the best set of decision rules for selecting women for dual-energy x-ray absorptiometry (DEXA) testing.[12]

The SCORE test generates a value based on the patient's age, weight, ethnicity, oestrogen use, presence of rheumatoid arthritis and history of fractures. The generated score results were tested against femoral neck BMD, and resulted in a high level of sensitivity (89%) and good specificity (50%). The ORAI test generates a value based on the patient's age, weight and oestrogen use. The generated score results were tested against hip or lumbar

Table 2. Statistically signficant risk factors for fractures in women 50-65 years of age

Risk factor	Relative risk for fracture (95%CI)	Risk factor	Relative risk for fracture (95%CI)	Risk factor	Relative risk for fracture (95%CI)	Risk factor	Relative risk for fracture (95%CI)
Age per 2 years[4]	1.11 (1.01–1.21)	HRT current use[8]	0.82 (0.74–0.91)	Alcohol ≥ 100g/wk[11]	1.70 (1.08–2.67)	Time since menopause 10–19 years[8]	1.18 (1.01–1.38)
Age per 5 years[5]	1.94 (1.55–2.42)	HRT per 5 y use[8]	0.5 (0.2–0.9)	Alcohol regular use[7]	1.4 (1.3–4.4)	Time since menopause 20–29 years[8]	1.31 (1.12–1.54)
BMI per increase of 10 kg/m² [5]	0.58 (0.36–0.92)	HRT > 2 y use[10]	0.44 (0.22–0.89)	Alcohol 1–6 drinks per week[8]	0.85 (0.75–0.96)	Time since menopause 30 years[8]	1.51 (1.26–1.81)
BMI ≥ 25.6 kg/m² Honkanen *et al*[4]	wrist 0.7 (0.5–0.9); ankle 1.6 (1.0–2.4)	Long history of HRT use[11]	0.70 (0.50–0.96)	Smoking current[4,8]	1.5 (1.3–1.5), 1.14 (1.00–1.30)	≥ 5 children[7]	2.5 (1.1–6.7)
BMI ≥28.6 kg/m² Honkanen *et al*[4]	wrist 0.5 (0.4–0.7); ankle 2.0 (1.3–3.1)	Diabetes mellitus[5]	9.17 (3.38–24.92)	Smoking former[8]	1.09 (1.00–1.19)	Oophorectomy before age 45 years[11]	3.64 (1.01–13.04)
BMI low[7]	1.1 (1.0–1.2)	Chronic conditions[4]	1.3 (1.1–1.5)	Smoking ≥ 11 cigarettes	3.0 (1.9–4.6)	African American ethnicity[8]	0.54 (0.41–0.72)
Height per 0.1 m[5]	1.58 (1.18–2.12)	Long-term work disability[4]	1.3 (1.1–1.6)	Disability pension[5]	3.79 (2.15–6.68)	Unmarried[5]	2.16 (1.28–3.64)
Mother with fracture[8]	1.27 (1.16–1.40)	Self-rated health (fair or poor)[9]	1.79 (1.52–2.11)	College education or higher[8]	1.26 (1.16–1.38)		
Grand mother with hip fracture[9]	3.70 (1.55–8.85)	Moderate daily physical activity[10]	0.61 (0.37–0.99)	Age at menopause[10]	0.94 (0.88–0.99)		

Abbreviations: BMI = body mass index; HRT = hormone replacement therapy

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spine BMD, and resulted in a high level of sensitivity (91%) and specificity of 41%.

Bone Density Tests

There are several tests to measure bone density, however the correlations between different tests is low. Dual energy X-ray absorptiometry (DEXA) is considered the gold standard since it is the most widely validated test against fracture outcome.[3]

Predicting fractures

Studies have indicated that probability of receiving a diagnosis of osteoporosis depends on the choice of the test and site, as well as the number of sites tested. A meta-analysis of 23 publications from 11 separate prospective cohort studies found that DEXA at the femoral neck predicted hip fracture better than measurements at other sites.[3] The study found that the pooled relative risk per decrease of 1 standard deviation in bone density was 2.6 (CI, 2.0–3.5).[3] The studies which were undertaken primarily in women in their late 60s or older also found that measurements at the femoral neck were comparable to forearm measurements for predicting fractures at other sites.[3]

The performance of peripheral densitometry at predicting fractures has been evaluated as part of the National Osteoporosis Risk Assessment study. Participants received baseline T-scores by measuring bone density at the heel (using single-energy x-ray absorptiometry or quantitative ultrasonography), forearm (peripheral dual-energy x-ray absorptiometry), or finger (peripheral dual-energy x-ray absorptiometry). The results varied by site and test type. Patients who were identified as osteoporotic by DEXA had higher fracture rates. Tests were not compared with DEXA of the femoral neck in this case, nor did the study describe results with respect to patient age or risk category.

However, another study comparing femoral DEXA with heel ultrasonography found that the latter was comparable to, but slightly worse than the hip measurement for women over 65 years of age. For women under 65 years, no comparison has been undertaken as yet.[3]

Treatment

Bisphosphonates such as alendronate and risedronate, hormone replacement therapy, raloxifene and calcitonin have been approved for use in the prevention or treatment of osteoporosis in Australia. Bisphosphonates are considered first-line for post-menopausal osteoporosis and have shown good efficacy, decreasing fracture risk by approximately 40–50% in women with low bone density,[3] with a good safety profile.[3] They have also shown benefits in terms of patient quality of life (reduced bed-day use), and decreased overall healthcare costs.[2]

A recent meta-analysis of 11 studies found that alendronate increases bone density in both early postmenopausal women as well as women with established osteoporosis, while reducing the rate of vertebral fracture over 2–3 years of treatment.[13] The meta-analysis included results from 12,855 women and examined the effect on vertebral fractures, forearm fractures, hip fractures as well as other non-vertebral fractures (**Table 3**).[13]

Table 3. Relative risk of fracture for patients on alendronate compared with those on placebo. (Evaluation from meta-analysis)[3,13]

Fracture location	Number of trials	Dosage	Relative risk
Vertebral fractures	8	≥ 5 mg	RR = 0.52 (CI, 0.43–0.65)
Forearm fractures	6	≥ 10 mg	Weighted RR = 0.48 (CI, 0.29–0.78)
Hip fractures	11	≥ 5 mg	Weighted RR = 0.63 (CI, 0.43–0.92)
Other non-vertebral fractures	6	10–40 mg	Weighted RR = 0.51 (CI, 0.38–0.69)

Criteria for initiating treatment can be difficult to determine. When deciding whether to initiate treatment, the physician is sometimes faced with decisions about whether more emphasis should be given to bone density measurements or the overall risk of fracture. Researchers have attempted to answer this question by evaluating data from trials of alendronate.[3] The study compared women with a similar overall risk for fracture but different bone densities, and whether they derived similar benefit from treatment. The Fracture Intervention Trial (FIT)[3] was conducted on two groups of participants. FIT-I was a placebo-controlled trial[14] on 2027 women over three years who had T-scores of -1.6 or lower at baseline, and pre-existing vertebral fractures. The FIT-II study[15] enrolled 4432 women and lasted for four years. The study evaluated women who had T-scores of -1.6 or lower, but without preexisting fractures at baseline.

The results of FIT-I show that postmenopausal women with low BMD and pre-existing vertebral fractures who received alendronate had a lower incidence of several types of fractures compared with women who received placebo (**Figures 1** and **2**).[14]

In the FIT-II study of women with low BMD, but no preclinical fracture, the incidence of fracture was dependent on the BMD score taken at baseline. Alendronate significantly reduced the risk of clinical fractures by 36% (relative risk (RR), 0.64 [CI, 0.50–0.82]) in women whose initial femoral neck score was –2.5 or less. In women with higher baseline BMD, however, alendronate did not significantly affect the risk

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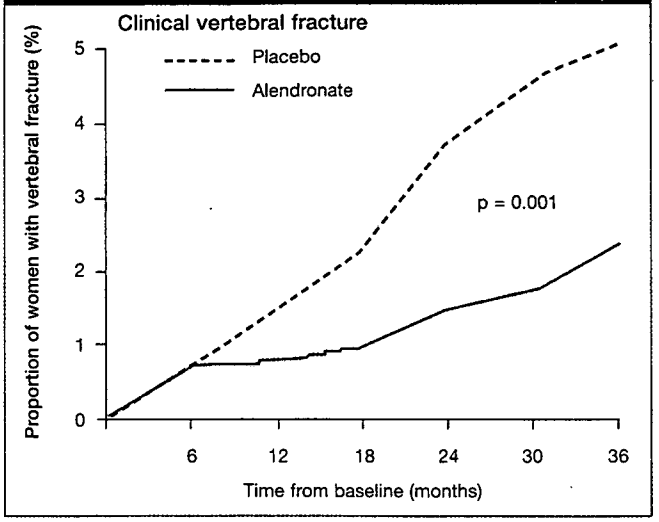
Figure 1. Cumulative proportion of women with clinical vertebral fracture



of fracture.

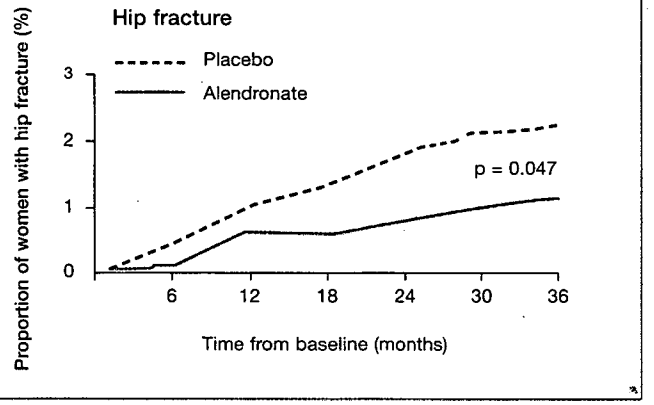
The results from these two studies[14,15] indicate that women who have more risk factors for fracture relating to bone structure and integrity such as age, very low bone density or preexisitng fractures, derive the most benefit from treatment.[3] The FIT study did not investigate other risk factors for fracture that are not related to bone structure, such as gait, psychomotor impairment etc, which may increase the risk of falling. A trial of risedronate, however, did examine these factors, and found that the drug had no effect on hip fracture rates in women ≥ 80 years with one or more risk factors for fall, but who did not necessarily have low BMD. Women in this study who were 70 – 79 years with T-score < –3, did benefit from treatment where hip fractures were reduced by 40% (RR, 0.6 [CI 0.4 – 0.9]).[3,16]

Harms

Not only do the therapeutic benefits and economic costs of screening and treating osteoporosis enter into the decision-making process, so do the potential harms of treatment and screening need to be taken into account. These may include:[3]

- the impact that a positive test result has on patients, producing anxiety, fear and the perception of vulnerability[3]
- the possibility of false reassurance if 'abnormal' results from previous year's DEXA tests appear improved on this year's normal calcaneal ultrasonogram
- potential deficit due to the time, effort and radiation exposure of repeated scans over years
- potential harms from inaccuracies and misinterpretations of bone density tests
- false-positives may lead to inappropriate treatment and false negatives may result in missed treatment opportunities[3]
- out-of-pocket costs to the patient of testing and treatments
- side effects of treatment.

Figure 2. Cumulative proportion of women with clinical hip fracture



Screening strategies

The authors of the screening study[3] estimated what effect screening 10,000 postmenopausal women would have on hip and vertebral fracture rates. This was undertaken at five-year age intervals using data for age-specific prevalence rates, treatment effects of alendronate based on trial results (risk reduction, 37% for hip fracture and 50% for vertebral fracture), adherence rates (estimated to be 70%). The resulting data for this analysis is presented in **Table 4**.

The data emerging on the risk/benefits of screening and treating osteoporosis indicates that the prevalence of the

Table 4. Screening for osteoporosis in 10,000 postmenopausal women: Hip and vertebral fracture outcomes by 5-year age intervals[3]

Variable	Age Group					
	50–54 y	55–59 y	60–64 y	65–69 y	70–74 y	75–79 y
Identified as high risk (T-score ≤ –2.5)	305	445	650	1200	2025	2850
Hip fractures prevented	1	2	5	14	39	70
NNS to prevent 1 hip fracture	7446	4338	1856	731	254	143
NNT to prevent 1 hip fracture	227	193	121	88	51	41
Vertebral fractures prevented	5	7	22	40	95	134
NNS to prevent 1 vertebral fracture	1952	1338	458	248	105	75
NNT to prevent 1 vertebral fracture	60	60	30	30	21	21

Abbreviations: NNS = number needed to screen; NNT = number needed to treat

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disease, the predictability of densitometry and the effectiveness of treatments tend to be lower for younger patients.[3] The authors of the screening study suggest that in the younger population of post-menopausal women, when deciding to whether to screen for osteoporosis, it is important to consider three consistent predictors of fracture; increasing age, low weight or BMI, and non-use of HRT (defined by current use, ever use or certain durations of use). The authors note that in the younger post-menopausal patient, the presence of one of these risk factors increases the probability of having osteoporosis by up to 100%, and increases the risk of fracture by 70% (RR, 1.7).[3]

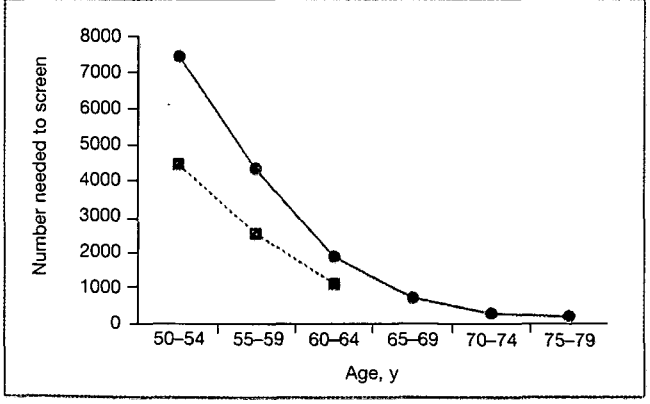
The presence of clinical risk factors such as these influences the outcomes from **Table 4**. For instance in the population of women 60–64 years, screening 10,000 women in this group results in prevention of five hip fractures over five years. However if the 10,000 women were nonusers of HRT, then the risk of fracture increases by 70%, meaning an incidence of nine hip fractures.[3] In the same way, the presence of such a risk factor decreases the NNS and NNT to prevent fractures as well (**Figure 3**).

The frequency of patient screening is also a matter that needs clarification in the literature. Estimations can be made based on the age-specific prevalence[3] and the precision of density tests.[3] Testing younger post-menopausal women could be done less frequently (eg. every five years) while older women, with whom there is a higher prevalence of osteoporosis should be tested more frequently (eg. every 2 years).[3] Once a woman has been diagnosed with osteoporosis, screening is no longer necessary.[3]

The authors of the screening study acknowledge that there are limitations to their findings, and stress the need for randomised controlled trials to look at screening strategies for osteoporosis. They acknowledge that assumptions were necessary in developing some of the recommendations (particularly **Table 4**) and stress that compliance in the clinical trial setting is different from clinical practice.[3]

The evidence arising from these studies does indicate that screening certainly does have a place in current clinical practice, and that this should be based on patient age and risk factors. There are several different therapies that have proven efficacy for the treatment and prevention of osteoporosis and resulting bone fractures. Alendronate has been shown to be effective at maintaining bone mineral density, as well as reducing the risk of fracture in vertebral and nonvertebral bone mineral.

Figure 3. Number needed to screen to prevent one hip fracture in 5 years.



The dotted line indicates women with at least one risk factor; the solid line indicates women without risk factors.

Practice points

- Among density measuring techniques, dual-energy X-ray absorptiometry (DEXA) at the femoral neck is the best predictor of hip fracture, and is comparable to forearm measurements for predicting fracture at other locations.
- Bisphosphonates decrease fracture risk by 40–50% in women with low bone density.
- Age-based screening is supported by prevalence data; the number needed to screen to prevent fracture decreases sharply with age in asymptomatic women.
- In younger asymptomatic women, consider risk factors, particularly:
  - increasing age
  - low weight.

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B&J Editorial

Joint Bone Spine 2001; **68**: 74-5

Iliac bone defects revealing systemic sarcoidosis

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(Submitted for publication July 17, 2000; accepted in revised form October 25, 2000)

Summary – Bone lesions are fairly uncommon in sarcoidosis (5 to 10% of cases). We report the case of a 40-year-old man in whom sarcoidosis of the lungs and bones was revealed by excruciating buttock and sacral pain. Computed tomography showed multiple punched-out defects in the left iliac bone. No similar cases have been reported in the literature. Joint Bone Spine 2001 ; 68 : 74-5. © 2001 Éditions scientifiques et médicales Elsevier SAS

bone / computed tomography / sarcoidosis

Sarcoidosis is a systemic granulomatous diseases that selectively involves the lungs [1]. Bone lesions are fairly uncommon (5 to 10% of cases) [1] and usually arise in the fingers, where they produce the 'tuberculoid osteitis' described by Jüngling [2] and now known as sarcoid dactylitis. We report an original case of systemic sarcoidosis of the lungs and bones revealed by excruciating pain in the buttocks and sacrum. Computed tomography showed punched-out defects in the left iliac bone.

CASE REPORT

This 42-year-old man with a smoking history of 30 pack-years but no significant health problems presented with excruciating pain in the left buttock (most marked laterally) and sacrum. The pain set in over a period of two months, with an inflammatory pattern, awakening the patient in the small hours of the morning. Nonsteroidal anti-inflammatory drugs were effective. Other symptoms were a fever of 38° C and weight loss of 2 kg. A physical examination failed to provide diagnostic orientation. The musculoskeletal system was normal, as was auscultation of the lungs. Laboratory tests showed mild inflammation (C-reactive protein, 25 mg/L; erythrocyte sedimentation rate, 40 mm/h; and fibrinogen, 4.5 g/L). The blood cell counts, serum electrolytes, and liver function tests were normal, as was the serum protein electrophoresis (no monoclonal component). Serum calcium was 0.96 mg/L. A chest radiograph showed interstitial disease in both lungs. Diffuse reticulonodular images were seen throughout the lungs on a computed tomography scan. Radiographs of the pelvis, sacrum, and hips were unremarkable. A whole body bone scan with images centered on the pelvis was normal *(figure 1)*. Computed tomography of the pelvis showed that the left iliac bone was riddled with punched-out defects about one millimeter in diameter *(figure 2)*. Examination of a biopsy specimen from one of these defects demonstrated a noncaseating epithelioid and giant cell granuloma (no foreign body or tubercle bacilli in smears or cultures). Bronchoalveolar lavage showed lymphocytic alveolitis (40×10^6 cells with 40% of lymphocytes and 60% macrophages) with no tubercle bacilli in smears or cultures. Gallium 67 scintigraphy disclosed heterogeneous diffuse hyperac-

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Figure 1. The whole body technetium scan was normal.

tivity of the lungs with no skeletal foci. Lung function testing found mild disturbances in CO diffusion (PaO_2 96 mm Hg, normal vital capacity, 10% decrease in the diffusing capacity of the lung for carbon monoxide). The diagnosis was systemic sarcoidosis involving the lungs and bones. Prednisone was given in a daily dosage of 30 mg. The buttock pain abated, the body temperature and C-reactive protein level returned to normal, and the pulmonary interstitial syndrome resolved. The bone images were unchanged at last follow-up six months after the initiation of prednisone therapy.

DISCUSSION

This histogically-documented case of systemic sarcoidosis had two highly unusual features, namely severe

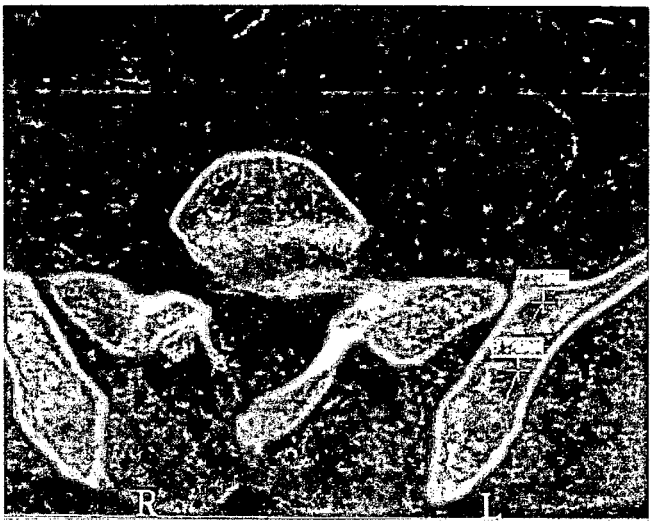

Figure 2. Computed tomography scan of the left iliac bone showing multiple punched-out defects about one millimeter in diameter.

buttock and sacral pain as the presenting symptom and multiple small punched-out defects on the computed tomography scan of the pelvis *(figure 2)*. These bone lesions were visible neither on the plain radiographs nor on the technetium or gallium scans, probably because these investigations are not sensitive for detecting lesions of barely one millimeter in diameter. This suggests that the rate of bone involvement in sarcoidosis may be underestimated. We are not aware of any similar reports in the literature. The diagnosis of sarcoidosis is rarely made as a result of the evaluation of bone lesions: these often escape notice or are overshadowed by manifestations of rapidly progressive systemic disease [1]. Furthermore, bone involvement in sarcoidosis is typically confined to the fingers and hands (metacarpal and carpal bones), where it produces defects of variable size and number; the feet are occasionally affected [1, 2]. Involvement of the spine [3], long bones, and skull vault [1] has been reported in a tiny number of patients.

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MSD.050.354.0019

Arthritis and anorexia?

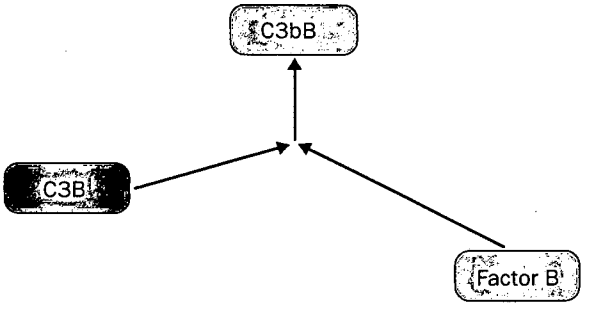
Lancet 2002; **360**: 1300

N Dalbeth, M Callan

A 34-year-old woman was assessed in January, 2002, for a 5-year history of intermittent pain and swelling affecting her hands, wrists, elbows, and ankles. She also described symptoms of Raynaud's phenomenon, hair loss, dry eyes and mouth, mouth ulcers, fatigue, and photosensitivity. However, the patient was most distressed by accusations by her friends of anorexia nervosa. She denied any alteration in her food intake. Since the age of 20 years, she had noticed thinning of her face and upper body. Her breast size had reduced from 38B to 34A. There was no change in her lower body size. She was previously well except for a history of presumed, but culture-negative, left hip septic arthritis in November, 1997. At that time, the admitting doctor recorded that she was "thin" and "drawn in the face".

Examination showed synovitis of her left wrist and left 2nd metacarpophalangeal joint. Schirmer test measured <5 mm in 5 min. Weight was 62·7 kg and height 172 cm (body-mass index 21). There was loss of subcutaneous fat in her face and upper limbs with normal fat distribution in the lower limbs. Radiographs of the hands and feet were normal. Blood tests showed ANA 1/320, ENA (including Ro and La) negative, rheumatoid factor 1/1260, C3 14 (65–190), C4 21 (14–40), and CRP <8. ANA screen in 1997 had been negative. Full blood count, midstream urine, and renal function were normal. C3 nephritic factor (C3NeF) was detected. The characteristic distribution of fat loss, low C3 and presence of C3NeF confirmed the diagnosis of partial lipodystrophy (PLD). This patient also meets diagnostic criteria for systemic lupus erythematosus (SLE) with photosensitivity, mouth ulcers, arthritis, and positive ANA. The presence of sicca symptoms, positive Schirmer test and RhF suggest a diagnosis of secondary Sjögren's syndrome. She has no features of mesangiocapillary glomerulonephritis type II (MCGN II), another condition that is strongly associated with C3NeF.[1] When last seen in July, 2002, her arthritis had improved on hydroxychloroquine.

MCGN II and PLD are associated with abnormalities in the alternative complement pathway. The alternative pathway C3 convertase C3bBb is formed when C3b binds to factor B to form the C3bB complex. Factor D then cleaves the bound factor B to form C3bBb (figure). C3NeF is an IgG autoantibody that stabilises C3bBb by protecting it from factor H-dependent dissociation. This stabilisation disrupts the normal physiological control of this pathway and leads to excessive activation of the alternative pathway with consumption of C3. Adipocytes are the major source of factor D.[2] Addition of C3NeF to adipocytes induces complement-dependent lysis of these cells in vitro. The presence of C3NeF in vivo is likely to have a similar effect.[3] The typical distribution of adipocyte loss in these patients may be due to a concentration gradient of factor D in the body, with greater amounts present in the adipocytes of the upper body.[4] Lupus-like illnesses have occasionally been reported in patients with C3NeF.[5] In most cases, the onset of SLE occurs years after onset of MCGN II or PLD. Therefore, it seems unlikely that C3NeF is primarily an SLE associated antibody. It is perhaps more plausible to suggest that C3NeF predisposes to the development of SLE by causing continuous tissue injury and auto-antigen release, or that common genetic or environmental factors play a role in the development of both.



Alternative complement pathway

Contributors
Both authors assessed the patient and wrote the manuscript.

Conflict of Interest statement
None.

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Lancet 2002; **360**: 1300

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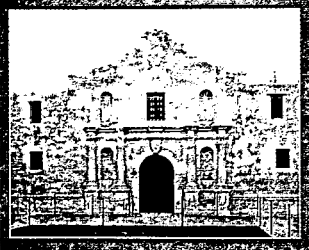
Conference highlights



24th Annual Meeting of the American Society for Bone and Mineral Research

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Vitamin B12 deficiency and low BMD

Citation

Low plasma vitamin B12 is associated with lower bone mineral density: the Framingham Osteoporosis Study

KL Tucker, MT Hannan, P Jacques *et al*

Background

Osteoporosis has been previously associated with pernicious anaemia. Vitamin B12 is thought to be important to osteoblast activity. A man with pernicious anaemia showed a significant improvement in bone density over two years of vitamin B12 treatment in one case report. Few studies, however, have examined vitamin B12 and BMD.

Methods

The study assessed the relationship between plasma vitamin B12 and BMD in 1144 men and 1487 women. From 1995–99, participants (30–87 years) had BMD measured with Lunar DPX-L at the hip (femoral neck, trochanter, Wards area, total hip) and lumbar spine. Plasma from the same examination was analysed for vitamin B12 by radioassay (Ciba-Corning). Subjects were divided based on standard cut-offs for vitamin B12: 200–250, >250–350, and >350 pg/mL. BMD measures were each regressed onto this categorical variable by sex, adjusting for age, BMI, height, smoking, alcohol use, calcium intake, vitamin D intake, physical activity score and season of measurement and least squares means were obtained. The study also regressed BMD onto each of the three higher categories relative to the lowest, separately for men and women.

Results

Five percent of men and 4% of women had B12 ≤ 200 pg/mL. These subjects had significantly ($p < 0.05$) lower BMD than at least two of the three higher categories as follows: Men: femoral neck, Ward's area and total hip, but not spine or trochanter; Women: trochanter, Ward's area, spine and total hip, but not femoral neck. As an example, for men, the LS means for total hip BMD for the four categories were 0.98, 1.02, 1.03, 1.03 g/cm^2, suggesting that vitamin B12 ≤ 200 pg/mL was associated with BMD about 5% lower than those above this cut point ($p < 0.05$ with the 3rd and 4th). For women, corresponding total hip BMD LS means were 0.676, 0.705, 0.703, 0.700 g/cm^2, $p < 0.05$ for 1st vs 3rd and 4th. Patterns were similar for other BMD sites.

Conclusion

These results support the hypothesised association between vitamin B12 deficiency and low BMD for both men and women in a population sample. Future studies should focus on B12 effects on bone biology, including the possibility that B12 effects are mediated directly or possibly through homocysteine metabolism.

Alendronate in reducing vertebral fractures in women with higher BMD T-scores

Citation

Alendronate reduces risk of vertebral fracture in women with BMD T-scores above -2.5: Results from the Fracture Intervention Trial (FIT)

D Black, D Thompson, S Quandt

Background

Alendronate has been shown to be effective in reducing risk of non-vertebral, hip and vertebral fractures among women with BMD T-scores below -2.5. However, several studies have suggested that bisphosphonates are less effective in reducing risk of non-vertebral and hip fractures among women with BMD above -2.5. The question of whether reductions in vertebral fractures depend on initial BMD has not been fully explored.

Methods

The researchers performed an analysis of data from the Fracture Intervention Trial (FIT) in order to examine whether reductions in vertebral fractures were larger in those with lower BMD. FIT was a randomised trial of 6459 women with femoral neck T-scores below -1.6 of whom 2027 had existing vertebral fractures. In this analysis, they combined data from women with and without existing vertebral fracture. Women were assigned to alendronate (5 mg for first two years, then 10 mg) or placebo and followed for an average of 3.8 years. They stratified the population according to initial femoral neck T-score into those with T-scores at or below -2.5 and those with T-scores above -2.5. They analysed the effect of alendronate on incidence of morphometric and clinical vertebral fractures within those strata.

Results

The researchers found no significant differences between the two groups in reductions of morphometric vertebral fractures or clinical vertebral fractures.

Results

	FN BMD T ≤ -2.5 (n = 2715)		FN BMD T > -2.5 (n = 3741)	
Type of fracture	N	RR (aln vs pbo)	N	RR (aln vs pbo)
Morph. Vertebral	214	0.50 (0.37, 0.67)	130	0.57 (0.39, 0.82)
Clincal Vertebral	78	0.62 (0.39, 0.98)	41	0.41 (0.21, 0.80)

Conclusions

They concluded that alendronate is effective in reducing the risk of both morphometric and clinical vertebral fracture in women with BMD T-scores above -2.5. There is no evidence that the effect of alendronate on vertebral fractures is different in those with lower BMD.

MSD.050.354.0022

Low BMD in rheumatoid arthritis

Citation

Bone mineral density in rheumatoid arthritis: disease-related variables associated with low bone mineral density
MC Lodder, Z de Jong, PJ Kostens *et al*

Aim

The aim of this study was to investigate the frequency of osteoporosis and variables associated with bone mineral density (BMD) in patients with rheumatoid arthritis (RA).

Methods

Three hundred and seventy-three patients participating in two research projects were investigated. The first project was the RAPIT trial, a study after the effect of frequent weight-bearing exercise versus usual care. The second project concerned a cohort of patients in clinical remission. Demographic and clinical data were collected and bone mineral density (BMD) was measured by means of dual X-ray absorptiometry (DEXA). Associations between demographic and clinical measure on the one hand and BMD on the other were investigated in single and multiple regression analyses.

The mean age (standard deviation) of the patients was 54 (12) years. Seventy-seven were females of whom 73% were premenopausal. The median (range) disease duration was 7 (1–50) years, and 66% were rheumatoid factor positive. Eighty-three percent had never used corticosteroids. The median Larsen score of hands and feet, reflecting radiographic joint damage, was 27 (0–155). The mean BMD at the spine (L1–4) was 0.99 (0.16) g/cm^2, while at the femoral neck the BMD was 0.78 (0.13) g/cm^2. Seven percent of the patients had osteoporosis of the hip and 13% osteoporosis of the spine (T score ≤ -2.5 SD).

Results and conclusion

High age, female sex, and low BMI are related to low BMD at the hip and spine. Participation in the RAPIT trial and a high Larsen score were significantly associated with low BMD at the hip. The study authors demonstrated an association between radiological RA damage and low BMD at the hip by presenting data on BMD in patients with RA.

Impact of BMD testing on treatment decisions

Citation

The influence of bone mineral density (BMD) testing on the treatment of osteoporosis in two Canadian non-academic community centres
EA Papadimitropoulos, ME Hamel, RJ Sebaldt *et al*

Aim

This prospective cohort study with 3-month follow-up was conducted to characterise the patients that Canadian physicians are referring for BMD testing and to assess the impact of the results on subsequent treatment decisions and lifestyle changes.

Methods

Testing was conducted in two Canadian non-academic centres, which included on-site and mobile dual-energy X-ray absorptiometry (DEXA) units. Recruitment for the study consisted of successive patients who were referred for BMD measurements at each of the two BMD testing sites over a 3-month period. Patient questionnaires were used to collect data on demographics, risk factors, medications and lifestyle. The BMD results were used to divide patients into three groups; osteoporotic, osteopenic and normal BMD according to WHO criteria. Based on BMD results, 23% of patients were osteoporotic, 46% were osteopenic and 31% had normal BMD. There was a positive correlation between number of risk factors and reduction in BMD from normal values. Application of the Osteoporosis Society of Canada practice guidelines, the National Osteoporosis Foundation guidelines or the Osteoporosis Risk Assessment Instrument, respectively, would have eliminated 45%, 13% and 43% of patients without osteoporosis that were referred for testing in the study and resulted in BMD testing for 53%, 85% and 78% of the patients with osteoporosis in the group. Following BMD testing, there was no significant change in patient-reported calcium intake or exercise, and 34% of patients felt that their knowledge of osteoporosis had increased. Three months after BMD testing, 60% of osteoporotic patients, 47% of osteopenic patients and 34% of patients with normal BMD were being treated with calcium, vitamin D or prescription medication.

Conclusion

Risk factors and current guidelines are entirely satisfactory in screening patients for BMD referrals. The results of BMD tests influence treatment decisions in the primary care setting although in this cohort of patients did not appear to have a significant effect on patients' lifestyle choices nor result in a reported increase in knowledge about osteoporosis in a majority of patients.

Vertebral fracture strategy in diagnosing osteoporosis

Citation

Assessment of densitometric criteria for the diagnosis of osteoporosis in men and women with vertebral fractures
L del Rio, N Guañabens, P Bassa *et al*

Aim

The aim of this study was to investigate the relations between bone mineral density (BMD) and vertebral fractures in men and women who attended the researchers' facility for their osteoporosis work-up.

MSD.050.354.0023

Methods
Treatment was started between four and 11 years of age (mean: 7y, 5m) and extended from four months to nine years (mean: 5y, 9m). Every patient received vitamin D (400 IU/day) and calcium supplements (750 mg/day). Growth was recorded at regular intervals. Bone mineral content (BMC) of the lower spine was measured and areal bone mineral density (aBMD) was calculated with a Hologic QDR 4500 DXA scanner, and repeated over a period of four years. Fractures were recorded and documented by X-ray. During the treatment period, 26 of the 46 patients (52%) suffered from 37 fracture events. Of these, 18 (39%) presented crush fractures of the vertebrae, and 19 episodes of long bone fractures occurred in 17 patients. Delay between treatment onset and the first fracture ranged between 22 months and 7 1/2 years (mean 4y, 6m). A total of 106 BMC measurements were performed in 46 patients between the ages of five years, 11 months and 17 years and five months.

Results
Over this age span, the aBMD did not increase. The aBMD Z score decreased from a mean of -2 SD at five years to reach -5 SD at 17 years of age. Repeated measurements in 37 patients at a mean interval of two years allowed the trial investigators to assess the longitudinal changes of the aBMD. In this subgroup, the aBMD Z score decreased from a mean of -2.59 SD to -3.27 SD ($p < 0.001$, paired T test) and the mean aBMD remained essentially unchanged at 0.480 g/cm^2. The mean BMC increased slightly from 15.71 to 16.12 g but the difference was not statistically significant.

Conclusion
The data enabled the investigators to conclude that skeletal complications in patients with DMD treated with OG are frequent and are associated with very low aBMD as calculated with DXA. If glucocorticoids are to be given to these patients, treatment to prevent bone loss should be started early. A study to evaluate the effectiveness and safety of such a preventive treatment should be initiated.

Long-term efficacy of alendronate

Citation
Ten-year efficacy and safety of alendronate in the treatment of osteoporosis in postmenopausal women
R Emkey, I Reid, A Mulloy *et al*

Background
Alendronate sodium (ALN), a specific inhibitor of osteoclastic bone resorption, reduced the risk of vertebral fractures and progressively increased BMD over three years in a study of 994 postmenopausal osteoporotic women. Previously, the researchers reported seven year results from 350 women who, after five years of continuous ALN treatment, participated in a double-blind two year extension (years 6–7), and now report the results for 247 women who entered an additional three year extension (years 8–10). During years 6–10, patients in the ALN 5 and 10 mg groups remained on their prior ALN dose. Patients in the ALN 20/5/placebo (A-PBO) group (20 mg for two years, 5 mg for three years) received placebo in years 6–10.

Results
A significant increase in spine BMD of 2.25% for ALN 10 mg and 1.60% for 5 mg groups was found during years 8–10. At the hip and total body, prior increases in BMD were maintained during years 8–10. Forearm BMD was stable with 10 mg but decreased slightly with 5 mg.

Women in the A-PBO group who had not been treated with ALN since the end of year 5 showed no significant change in BMD at both spine and total body, but small decreases in hip and forearm BMD occurred during years 8–10. Cumulative 10 year spine BMD increases were 13.7% with ALN 10 mg and 9.8% with 5 mg.

After the initial 18 months, each additional year of treatment with ALN 10 mg increased spine BMD by 0.73% vs. 0.57% with ALN 5 mg. The safety and tolerability profiles of ALN 5 and 10 mg were similar to placebo during both years 8–10 and years 6–10.

The three year incidences of non-vertebral fractures during years 8–10 were 8.1, 11.5, and 12.0% in the ALN 10 mg, 5 mg and A-PBO groups. The 3 year incidences in the original cohort during years 1–3 were 8.5% (pooled ALN) and 10.7% (placebo).

Although patients were older in years 8–10, the expected age-related increase in fracture risk was not observed. Neither stress fractures nor fracture malunion were reported.

Conclusion
The investigators concluded that ALN treatment is effective for 10 years and is generally well tolerated. Spinal BMD continues to increase over 10 years and other skeletal benefits are maintained.

Non-vertebral fracture data indicate no change in risk over time, and suggest that fracture risk reduction is maintained during continued treatment. Discontinuation of ALN after five years leads to bone loss at non-spine sites, and continued treatment with ALN through 10 years yields sustained skeletal benefits.

MSD.050.354.0024

Vitamin D depletion and osteoporosis

Citation

Prevalence of vitamin D depletion among subjects seeking advice on osteoporosis: A five-year cross sectional study with therapeutic and public health implications
N Parikh, T Eskridge, J Hill *et al*

Background

There is continued concern about vitamin D depletion in the US population. The researchers had previously reported that a significant proportion of patients seeking advice for osteoporosis are vitamin D depleted. Since then concerted public health education efforts about calcium (Ca) and vitamin D nutrition have occurred. They therefore assessed the impact of such efforts on the prevalence of vitamin D depletion among individuals attending their osteoporosis clinic.

Methods

The computerised database of all patients seen between January 1997 and December 2001 was reviewed for the prevalence of vitamin D depletion (defined as serum 25-OHD of ≤ 15 ng/mL). They excluded patients with obvious known causes for vitamin D, and all Hispanics and Asians (n = 201). Serum Ca, creatinine (Cr), PTH and 25-OHD were measured in all patients.

During the five years, 3790 new patients were seen; 3343 (88%) were women and 3195 (84%) were whites. The mean age was 65 ± 13 years. For the entire study cohort the prevalence of vitamin D depletion was 20% (748/3790) and remained constant during the five years (17%, 21%, 18%, 18%, and 24% respectively).

Results

Vitamin D depletion was higher in blacks than in whites (43% vs 16%; $p < 0.001$). Serum 25-OHD correlated with PTH ($r = -0.22$; $p < 0.001$) but not with age, Ca, or Cr. Age and serum 25-OHD, Ca and Cr all predicted PTH level, but serum 25-OHD and Cr were the strongest predictors (T statistic -13.7 and +17.7 respectively). Based on the differences in slopes of PTH on 25-OHD, black women had a greater increase in PTH than white women (-1.23 vs -0.79)

Conclusion

This is the largest study of its kind in the US and confirms the preliminary findings of the researchers' two-year study. Indeed, they observed a disturbing upward trend (about 2%–5%) in vitamin D depletion over the five years despite an explosion of public education efforts. This implies that either these efforts are ineffective, or that foods and supplements contain inadequate amounts of vitamin D, or both. Vitamin D depletion is prevalent among ambulatory patients seeking advice about osteoporosis. Since poor vitamin D nutrition may adversely affect response to specific osteoporotic therapy, greater attention to vitamin D nutrition in addition to Ca is essential. The lack of decline in the prevalence of vitamin D depletion over five years implies that current efforts are ineffective and need reexamination.

Lack of follow-up for patients with osteoporotic fractures

Citation

Osteoporosis Fracture Tracking Study: Medical care is often delayed for patients of orthopaedic surgeons
JG Skedros

Background

Patients with osteoporotic fractures typically do not receive subsequent medical treatment for osteoporosis. The researchers hypothesised that even if patients with osteoporotic fractures were specifically referred to their primary care providers (PCPs), the majority would not be treated within 84 days (12 weeks) of fracture.

Methods

They evaluated the effectiveness of 14 surgeons in facilitating a timely PCP visit for their patients. Participating orthopaedic surgeons received remuneration for each patient completing the study. Patients who qualified were > 50 years old, had an apparent osteoporotic (low-energy) fracture, and had no prior treatment for osteoporosis. Two letters requesting a PCP appointment were sent: the first letter within 10 days of fracture, and the second letter 3–10 weeks after fracture. Patients were also: 1) informed that they may have osteoporosis and may be at risk for subsequent fracture, and 2) instructed to make a PCP appointment for possible further work-up and treatment.

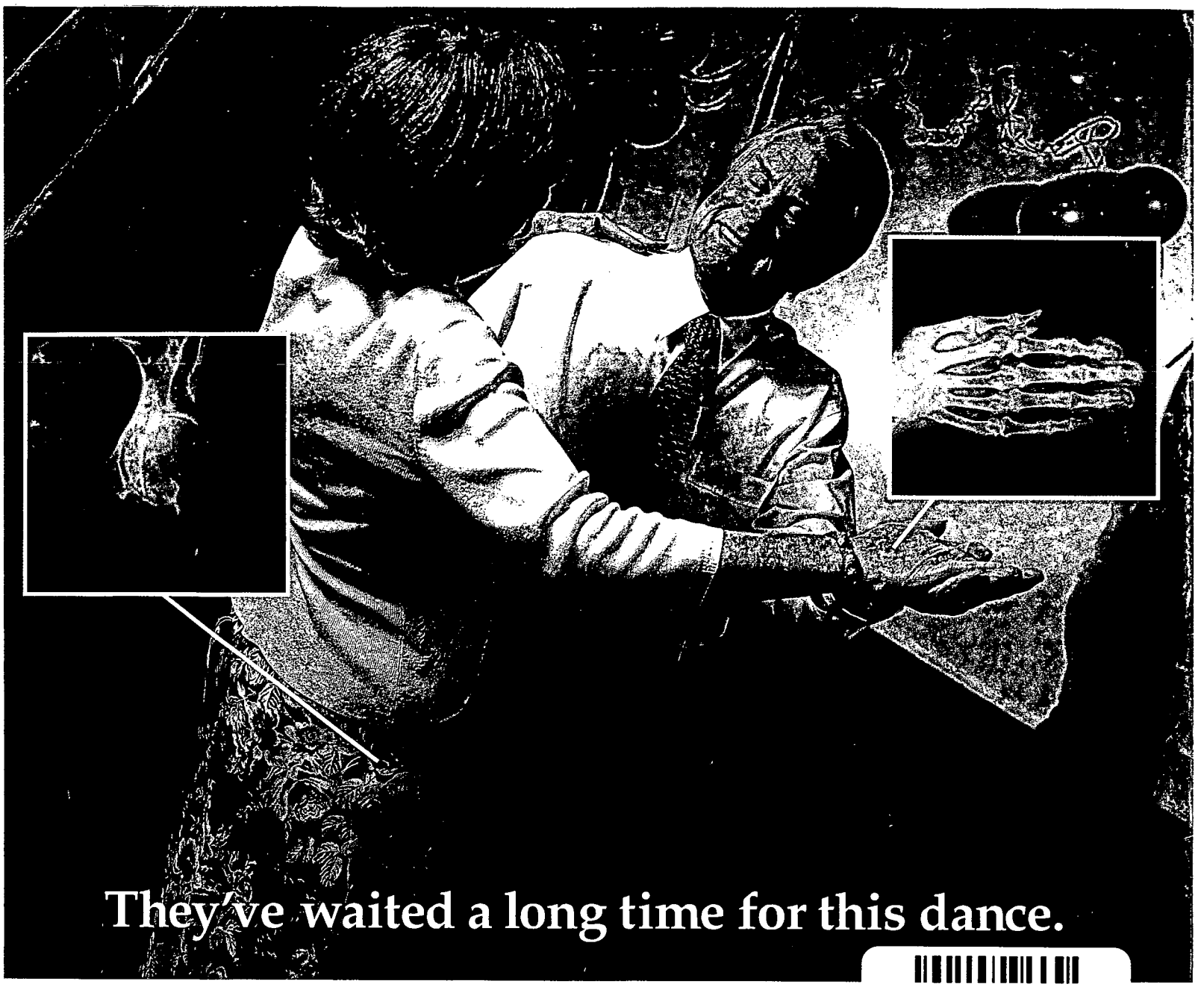
Results

Results showed that of 55 patients (48 females, 7 males: mean 70.8, range 51–90), 23 (42%) were not seen by a PCP within 84 days. Thirty-two (58%) patients saw a PCP within 84 days, but osteoporosis was not addressed in four patients (average days to PCP, 38: range 7–71 days). Of patients seen within 84 days, pharmacologic treatment (eg, oestrogen, bisphosphonate, etc) was started in 19 (59 %), but typically not within 37 days of fracture. Of the 14 participating orthopaedic surgeons, five were non-compliant and six were inconsistent in their participation, forgetting to send the letters and to inform their patients to make a PCP appointment.

Conclusion

These results indicate that standing discharge hospital orders (for medications, PCP follow up, bone density scanning, etc.) may be more effective in achieving timely medical treatment for patients with osteoporotic fractures.

MSD.050.354.0025



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1 Cannon GW et al Arth & Rheum 2000; 43(5): 978-987. 2 Langman MJ et al JAMA 1999; 282(20): 1929-1933. 3 Bombardier C et al N Engl J Med 2000; 343: 1520-1528. 4 Zacher J et al Curr Med Res Opin 2002; 18(4): 229-236. * ibuprofen, diclofenac and naproxen.

PBS Information: Restricted benefit. Symptomatic treatment of osteoarthritis.

Note: The use of rofecoxib for the treatment of the following conditions is not subsidised through the PBS: acute pain, soft tissue injury, arthrosis without an inflammatory component.

VIOXX® (rofecoxib, MSD) **Use:** COX-2 inhibitor, Osteoarthritis and Rheumatoid Arthritis. **Contra:** Active peptic ulcer; GI bleeding; asthma, urticaria or other reactions to NSAIDs incl aspirin; concomitant NSAIDs. **Prec:** History of peptic ulcer; GI bleeding; high dose, prolonged use; alcoholism; dehydration; asthma; oedema; hypertension; heart failure; infection (masks fever); hepatic, renal impairment; elderly, debilitation; pregnancy, lactation, children. **Adverse:** GI upset include perforation, ulceration, bleeding; anaphylactoid reactions (possible); hepatic and renal effects; anaemia; fluid retention; hypertension; confusion; rash; others, see full PI. **Interact:** Steroids, anticoagulants; smoking (incr. risk of GI event); hepatic enzyme inducers e.g. rifampicin; theophylline; drugs metabolised by CYP1A2 e.g. amitriptyline, tacrine; ACE inhibitors; aspirin; lithium; diuretics (possible). **Tablets:** Rx Rofecoxib; lactose; cream (12.5 mg); yellow (25 mg); Packs [30]. **Dose:** OA, 12.5 – 25 mg once daily; RA, 25 mg once daily. **Dispensing Price:** 12.5 mg, $29.48; 25 mg, $42.79. **Refer to full Product Information before prescribing. Product information is available directly from Merck Sharp & Dohme or by reviewing MIMS CD of MIMS Annual, 2003.**

MERCK SHARP & DOHME

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