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Guidelines for treatment of osteoporosis in men

BACKGROUND  Osteoporosis is associated with significant morbidity and mortality in men. Published randomised controlled trials assessing the benefits of therapy in men with osteoporosis are limited, but those available need to be used to develop management guidelines.

OBJECTIVE  To present evidence-based guidelines for the treatment of osteoporosis in men.

DISCUSSION  It is estimated that 30-40% of men presenting with spinal fractures have another illness contributing to their bone disease. Therefore assessment and treatment of coexisting medical conditions is a vital part of management of osteoporosis. While primary prevention of fractures remains crucial, treatment to ensure further fractures do not occur is equally important. Alendronate is the treatment of choice for men with osteoporosis and fractures, with cyclical eltrocalcitone an appropriate alternative and testosterone replacement therapy is indicated in hypogonadal men presenting with osteoporosis.

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While there are many published randomised control trials assessing the benefits of therapy for postmenopausal osteoporosis, these are limited in men.

In order to develop the following guidelines for the management of osteoporosis in men, all published manuscripts and abstracts over the past 20 years, relating to the treatment of osteoporosis in men were enlisted through a systematic search of Medline, Current Contents, CINAHL and Cochrane Library. We also scanned the bibliographies of included studies for additional references and abstracts presented at the Annual Meeting of the American Society for Bone and Mineral Research and the International Bone and Mineral Society. Only publications relating to the treatment of osteoporosis in men were evaluated. By using the level of evidence according to the NH&MRC criteria (Table 1), an algorithm was devised for the most appropriate treatments of osteoporosis in men (Figure 1).

The following treatment strategies are presented according to the level of evidence based on randomised controlled trials (RCTs). While only studies pertaining to the treatment of osteoporosis in men were sought, this has occasionally proven difficult and where specified, the combined treatment data for both men and women has been presented. Studies relating to the treatment of glucocorticoid induced osteoporosis in men are discussed elsewhere in this journal.

General measures

These include recommendations for lifestyle modification discussed in the previous article (pp. 781-785). One systematic review (15 RCTs, 1054 patients, predominantly women. E1) found that nutritional supplementation (oral protein and energy feeds) reduced unfavourable outcomes after a hip
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Table 1. Levels of evidence according to the NH&MRC
- Level 1 (E1) evidence obtained from a systematic review of all relevant randomised controlled trials.
- Level 2 (E2) evidence obtained from at least one properly designed randomised control trial.
- Level 3 (E3) evidence obtained from a well designed pseudo randomised controlled trial.
- Level 4 (E4) evidence obtained from case series, either pre-test or post-test and post-test.

Clinical presentation

Any fracture
After minimal trauma

Suspected vertebral fracture
- kyphosis
- height loss
- back pain

Major risk factors for fracture
- hypogonadal
- corticosteroid use
- family history of osteoporotic fracture
- low body weight
- smoking
- recurrent falls

Other risk factors for fracture
- lifestyle factors: low calcium intake, physical inactivity, smoking, excess alcohol
- medical conditions predisposing to osteoporosis*

Investigation

Ensure adequate calcium, vitamin D

Management

Treatment of osteoporosis to prevent (further) fracture
1st line therapy†
- alendronate or risendronate
2nd line therapy
- etidronate
if hypogonadal# consider testosterone

Consider prevention of bone loss
- alendronate
- etidronate
if hypogonadal consider testosterone

Reassure and follow up in 2-5 years

Fracture. There are no reports relating to nutritional supplementation and either changes in bone mineral density (BMD) or fracture rates in men.

Falls prevention and rehabilitation programs
These may be beneficial for elderly men with multiple risk factors for falling. The overall evidence (18 RCTs, predominantly women, OR=1.72; 0.78-3.75) for effectiveness of geriatric orthopaedic rehabilitation units is inconclusive (E1). A recent analysis suggested that there is inadequate evidence for the effectiveness of single interventions such as exercise alone or health education classes for the prevention of falls (E1).

Hip protectors
Most hip fractures occur as a result of a fall or other traumatic event resulting in direct impact onto osteoporotic bone. Hip protectors reduce the risk of hip fracture within a selected population (frail and elderly) at high risk of sustaining a hip fracture. The cost effectiveness is unclear.

Acceptability by the users of the protector remains a problem, with poor long term compliance (7 RCTs, 3553 patients predominantly women, E1).
In a study of 392 men and 1409 women aged 70 years and older, hip protectors significantly reduced the risk of hip fractures (13 subjects in the hip protector group had a hip fracture, as compared with 67 subjects in the control group; RR=0.2, 95% confidence interval 0.05-0.5).  

**Medications**  
**Bisphosphonates**  
Bisphosphonates are potent inhibitors of bone resorption. There are numerous studies reporting the benefits of alendronate and risedronate for the treatment of postmenopausal osteoporosis (E1). Published data in men has only recently become available. Currently four bisphosphonates are available for the treatment of osteoporosis in men in Australia.  

**Alendronate**  
Alendronate (Fosamax) is an amino-bisphosphonate, which does not impair mineralisation. There are two RCTs assessing the antifracture efficacy of alendronate in men. In one RCT1 (146 alendronate treated and 95 controls, aged 31-87 years, randomised for two years, E2) alendronate 10 mg daily significantly reduced spinal fracture rates (0.8 versus 7.1%; P=0.02). All subjects received daily calcium (500 mg) and vitamin D3 (400-450 IU). In the other RCT (68 alendronate treated and 65 alfalcacidol treated men, two year open label randomised study, E3) there were five subjects with spinal fractures in the alendronate treated group and 10 in the alfalcacidol treated group (P=0.04). These are the only published studies powered adequately to demonstrate antifracture efficacy in men with osteoporosis (defined as a BMD t-score <-2.5).  

To our knowledge, there are six RCTs (348 alendronate treated and 277 controls, E3) evaluating the effects of alendronate on BMD in men with osteoporosis. Spinal and femoral neck BMD increased over a 1-3 year treatment period by 6-10% and 2.5-5.0%, respectively. There is no published BMD data comparing the effects of alendronate 10 mg daily to alendronate 70 mg once weekly on BMD in men with osteoporosis.  

Alendronate has been associated with dyspepsia, abdominal pains and oesophageal ulceration in women, but this does not appear to present a major problem in men.  

Cyclical etidronate (Didrocal)  
There are no RCTs assessing the antifracture efficacy of cyclical etidronate in men with osteoporosis, except in glucocorticoid induced osteoporosis (E2). There are nine RCTs (300 subjects, in open labelled studies with no case controls, E3) in men with osteoporosis treated with cyclical etidronate. In all studies, significant increases in spinal BMD (3-9%) were noted over a 2-5 year treatment period, without consistent changes in femoral neck BMD.  

Etidronate is used in a cyclical regimen (400 mg daily for 14 days of every three monthly cycle) so as to prevent a mineralisation defect which may occur if administered continuously. It has been reported to cause mild inflammation in the lower, but not upper gastrointestinal tract.  

**Pamidronate**  
Pamidronate (Aredia) is approved for the treatment of osteoporosis in men with myelomatous bone disease (S-100 scheme). There is one RCT (E2) performed in patients (108 pamidronate treated men) with lytic myelomatous bone disease, demonstrating significant reductions in skeletal events (pathological fractures, hypercalcaemia and the need for radiotherapy or surgical intervention). Other RCTs demonstrating increases in BMD with pamidronate have been performed in men with osteoporosis receiving glucocorticoid therapy and undergoing transplantation (E4).  

**Risedronate**  
Risedronate is the most potent of the four bisphosphonates listed. There is one RCT (E2), assessing the role of risedronate in glucocorticoid induced osteoporosis.  

**Calcium and vitamin D**  
Calcium and vitamin D are weakly antiresorptive. There are no RCTs assessing the antifracture efficacy of calcium and vitamin D3 in men with osteoporosis. There are three RCTs (456 treated and 456 controls) assessing the role of calcium and vitamin D on fracture prevention in ‘healthy’ elderly men (E2). In all three, the primary endpoint was spinal fractures. Unfortunately, when the data was analysed separately for men, the beneficial effect on fracture reduction was lost due to low fracture rates. Moreover, in one of the RCTs (333 men randomised to vitamin D3 400 units daily and 329 to placebo) fracture rates were significantly affected by a large proportion of the men who were receiving vitamin supplements before enrolment.

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**Guidelines for treatment of osteoporosis in men**

**Table 2: Men requiring specialist treatment**

Referal to specialist bone centres is appropriate in the following circumstances:

- Men with osteoporosis who have complex medical conditions
- Young men (<50 years) who present with severe osteoporosis
- Men who present with history of numerous or recurrent fractures
- Men with osteoporosis who show inadequate response to therapy
- Men who experience problems or side-effects with treatment
- Men who present with an acute spine fracture susceptible to therapy by percutaneous vertebroplasty

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There are two RCTs\(^{29,30}\) (123 treated and 127 control, E2) demonstrating a positive effect of calcium and vitamin D on femoral neck BMD in community dwelling men aged 60 years and older. In one study,\(^{29}\) men were randomised for four years to daily calcium 750 mg, 25 hydroxyvitamin D\(_3\) 15 \mu g or placebo, while in the other study,\(^{30}\) men were randomised for three years to either daily calcium 500 mg and vitamin D\(_3\) 700 units or placebo. In a third RCT\(^3\) (E2), no beneficial effect on either radial or spinal BMD was found in a younger cohort (41 treated and 36 controls) who were treated for three years with daily calcium 1000 mg and vitamin D\(_3\) 1000 units. There are no RCTs assessing BMD changes in men with osteoporosis treated with calcium and vitamin D\(_3\) alone.

Until studies which are powered adequately to predict fracture prevention are presented, daily supplementation with calcium (1500 mg) and vitamin D\(_3\) (400 units if serum 25 hydroxyvitamin D levels less than 40 nmol/L) must be considered an important adjunct to other therapeutic interventions such as alendronate, etidronate or testosterone.

Calcitriol (rocaltrol)
Calcitriol is the active hormonal form of vitamin D and has been approved for the treatment of osteoporosis in men with fracture (PBS authority required). This form of therapy is not common practice in other countries. In a small cohort of men with cirrhosis\(^3\) (E4), calcitriol prevented spinal bone loss over 12 months. In the only published RCT in men with osteoporosis\(^9\) (20 treated and 19 controls, two year study, E3), calcitriol (0.25 mg twice daily) was no better than calcium (1000 mg daily) alone for the prevention of fractures. Bone mineral density remained unchanged in the calcitriol treated subjects, but increased by 2–3% in the calcium treated subjects.

Current evidence suggests that calcitriol is unlikely to be beneficial for treating men with idiopathic osteoporosis. Furthermore, there is an associated risk of hypercalcaemia and hypercalciuria with doses of 0.5 \mu g daily or more.\(^9\)

Testosterone

Up to 16% of men with spinal fractures have evidence of hypogonadism.\(^4\)

Testosterone therapy and its effect on BMD are largely dependent on:
- gonadal and growth status of the individual
- the duration of pre-existing hypogonadism
- the degree of osteopenia and
- the duration of testosterone therapy.\(^2,5\)

There are no published studies demonstrating antifracture efficacy with prolonged testosterone therapy.

In men with hypogonadism

There are two RCTs\(^{30,31}\) (21 men in one study and eight in another, aged 19–53 years, E4), demonstrating the effects of testosterone replacement in men with delayed puberty (idiopathic hypogonadism): Significant (600 mg every 4–6 months) increases in both cortical and trabecular bone density was observed, with maximal responses occurring in those whose epiphyses had not yet fused.

There are six RCTs\(^{32–37}\) (73 men with acquired hypogonadism, E3) assessing the role of testosterone replacement (intramuscular injection) on BMD in hypogonadal men. Significant increases in spinal BMD as measured by both dual energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) (5–15%) and increases in muscle strength were observed over 18–24 months. No significant changes in cortical BMD were noted.

In men with normal testosterone levels

There is only one RCT\(^{38}\) (21 men aged 34–73 years, E4) assessing the role of testosterone therapy (intramuscular injection) in men with osteoporotic spinal fractures and normal testosterone levels. Six months of therapy resulted in a 5% increase in spinal BMD (E4). There are eight RCTs\(^{39–46}\) (76 men, aged 65 years and older, E2) assessing the role of testosterone therapy (intramuscular, transdermal or sublingual) in normal elderly men. Decreases in fat free mass accompanied by increases in lean mass were apparent after a 3–36 month treatment period. No significant changes in muscle strength were observed, while only modest increases in spinal BMD (<2%) were reported.

Other weaker androgens such as nandrolone (one RCT,\(^a\) 21 men) have been studied in eugonadal men with osteoporotic fractures but without any beneficial effect (E4).

Administering testosterone

Testosterone replacement can be adequately achieved by the transdermal route (androderm patch 12.5 mg twice daily), intramuscular injections (depot testosterone or sustanon 250 mg every 2–3 weeks) or by subcutaneous implants (600 mg every 4–6 months).\(^{32–37}\)

Testosterone therapy is available for men with proven androgen deficiency due to testicular or pituitary origin (PBS authority required). While all forms of testosterone supplements appear to be well tolerated, their long term safety remains unclear. The risk of prostatic disease in eugonadal men is uncertain.\(^3\)

Due to reported cases of prostatic carcinoma occurring with prolonged testosterone therapy, regular digital examination of the prostate and monitoring of serum prostate specific antigen activities is required.

Other therapies
Calcitonin by subcutaneous injection (100 units every three weeks) reduced bone turnover in 12 castrated men in one RCT\(^{38}\) (E3) and increased total body...
and spinal BMD in 17 men with idiopathic osteoporosis in two other RCTs (E3).\textsuperscript{4,5}

Parathyroid hormone administered by subcutaneous injection (RCT,\textsuperscript{10} 10 men versus 13 controls, E2) significantly increased lumbar spine BMD by 13.5% and femoral neck BMD by 2.9% over an 18 month study period (P<0.001 and P<0.05 versus controls respectively).

The role of growth hormone and insulin growth factor therapies in male osteoporosis remains unproven. In one RCT\textsuperscript{11} (21 elderly men aged 60 years and older), spinal BMD increased by 1.6% after six months of subcutaneous growth hormone therapy (0.03 mg/kg every three week, E3). The value of fluoride and strontium therapies in male osteoporosis should be considered as experimental only.

Monitoring therapy

After initiation of therapy, it is important to monitor patients\textsuperscript{4} to ensure that bone loss is controlled. Serial dual energy X-ray absorbiometry measurements are useful for monitoring the efficacy of therapy because of their excellent precision, convenience and rapid scanning times.\textsuperscript{9,13} It is recommended that BMD should be performed at baseline and after one year of initiating therapy. Thereafter, biannual DXA assessments are usually carried out to monitor response to therapy. Repeat measurements should be performed on the same machine for monitoring. Absolute BMD values (in g/cm\textsuperscript{2}) and not t-score values should be compared with repeated measurements. A positive response is regarded as a change in BMD equal to twice the precision error of the machine (usually 1% for the lumbar spine and 0.9% for the total femoral neck BMD).\textsuperscript{21} Biochemical measurements of bone turnover\textsuperscript{21} may become useful in the future for the management of the individual patient, but their role has yet to be established.

Conclusion

It is currently unknown what percentages of men with osteoporosis are receiving therapy. The present recommendation is to treat all men with BMD t-score values less than -2.5 and with a history of osteoporotic fractures.\textsuperscript{6,8} At present RCTs suggest that alendronate, followed by cyclical etidronate are the drugs of choice for men with osteoporosis. General measures together with adequate calcium and vitamin D supplements (if required) are always recommended. Testosterone replacement therapy is indicated in men with hypogonadism (serum total testosterone concentration less than 8 nmol/L).

Secondary causes of osteoporosis should always be defined and specific disease processes treated appropriately. Specialist referral may be necessary for patients with complex medical problems, severe osteoporosis, side effects from medication, or for those who do not respond to the first line measures (Table 2).

References

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