Treatment of osteoporosis in men with bisphosphonates: rationale and latest evidence

Ie-Wen Sim and Peter R. Ebeling

Abstract: Osteoporosis in men contributes to significant morbidity and mortality. Hip fractures in men are associated with greater mortality compared with women, with a mortality rate of up to 37.5% within a year following the fracture. Its timely diagnosis and treatment are therefore essential. However, despite one-third of all hip fractures worldwide occurring in men, osteoporosis in men remains an immensely under-recognized and undertreated public health problem. Bisphosphonates are well studied first-line treatments for postmenopausal women with osteoporosis and have been shown to reduce fragility fractures at all clinically important sites (vertebral, nonvertebral, hip and wrist). However, the majority of studies of oral or intravenous bisphosphonate therapy in men with osteoporosis report effects on surrogate markers, including bone mineral density (BMD) and biochemical bone turnover markers, rather than on fragility fractures. Oral or intravenous bisphosphonate therapy increases spinal, total hip and femoral neck BMD compared with placebo in men with osteoporosis. Both bone resorption and bone formation markers are decreased following bisphosphonate therapy, with the onset of the decrease in bone formation markers being delayed. In a study of intravenous zoledronic acid given to older men and women following a hip fracture, any clinical vertebral and nonvertebral fractures were all reduced compared with placebo infusions. In addition, mortality was reduced in patients who received zoledronic acid.

Recent studies in men with osteoporosis have increasingly reported reductions in incident vertebral fractures with oral or intravenous bisphosphonate therapy, although all studies have been underpowered to detect effects on nonvertebral and hip fracture outcomes. Bisphosphonates have a role as monotherapy, as consolidative therapy after a course of teriparatide therapy, or in combination with testosterone replacement in men with hypogonadism and osteoporosis. Bisphosphonate therapy is validated and important in the treatment of osteoporosis in men.

Keywords: alendronate, bisphosphonates, hypogonadism, osteoporosis, risedronate, zoledronic acid

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Introduction

Osteoporosis remains an immensely under-recognized and undertreated cause of morbidity and mortality in men, with one-third of all hip fractures worldwide occurring in men [Gullberg *et al.* 1997]. One in six men will sustain a hip fracture by the age of 90 [Nguyen *et al.* 1996], with almost half of these occurring before the age of 80 [Chang *et al.* 2004]. Up to 40% of hip fractures in men occur in residential care, and one-fifth of those who sustain a hip fracture will subsequently have a second hip fracture. Importantly, hip fractures in men are associated with greater mortality compared with women, with a mortality rate of up to 37.5% within a year of fracture [Cooper *et al.* 1992; Jones *et al.* 1996; O'Neill *et al.* 1996; Orwoll and Klein, 1995].

Vertebral fractures are also common among older men and are strongly associated with subsequent hip and nonvertebral fractures. Although the majority of vertebral fractures are painless,

they can impart significant morbidity, including height loss, reduced quality of life, respiratory dysfunction and social withdrawal [Khosla *et al.* 1994; Orwoll and Klein, 1995]. Vertebral fractures tend to occur earlier in men than women, with a peak incidence in the fourth and fifth decades of life [Cooper *et al.* 1992; Jones *et al.* 1996; O'Neill *et al.* 1996], whereas above the age of 65, incidence rates of vertebral fractures in men are half those in women. The incidence of vertebral fractures at a younger age in men may be partially accounted for by traumatic fractures.

Despite the considerable health burden of fractures and osteoporosis in men, there is a paucity of reported clinical studies that explore the efficacy of osteoporosis therapy in men as opposed to postmenopausal women, particularly with regards to fracture reduction as a primary outcome [Boonen *et al.* 2009; Orwoll *et al.* 2000, 2010a, 2010b]. Increasingly, recent data support the role of bisphosphonate therapy in the treatment of osteoporosis in men.

Aetiology of bone loss in men

Bone mass and strength are determined by numerous factors, including the attainment of peak bone mass and subsequent age-related bone loss; both processes being dependent on sex steroid production and action. Notably, the majority of nonvertebral fractures occur in men without osteoporosis, implying that other factors distinct from bone mineral density (BMD) contribute to fracture risk [Seeman *et al.* 2006].

Natural history of bone loss in men

Analogous to the process in women, both cortical and trabecular bone density increase significantly during puberty in response to the actions of sex steroid hormones [Krabbe *et al.* 1984]. In particular, testosterone exerts an indirect effect on bone, through the skeletal aromatization of testosterone to oestrogen [Ebeling, 1998]; mutations of the aromatase enzyme have been associated with severe osteoporosis in men [Morishima *et al.* 1995; Smith *et al.* 1994]. The finding of low bone mass in men with idiopathic hypogonadotropic hypogonadism further emphasizes the role of sex steroid hormones in attainment of optimal peak bone mass [Finkelstein *et al.* 1987].

Bone loss commences soon after peak bone mass is achieved [Nordstrom *et al.* 2007], with longitudinal studies suggesting that the rate of loss accelerates after the age of 70 in men [Jones *et al.* 1994; Szulc and Delmas, 2001]. In older men, bone formation markers remain stable or decline slightly, whereas bone resorption markers increase, mainly after age 70, indicating a likely role for antiresorptive therapy, such as bisphosphonates. This increased bone resorption may be related to low levels of bioavailable oestradiol and testosterone [Pietschmann *et al.* 2001]. In men over age 65, rapid bone loss is more common in men with testosterone or oestradiol deficiency compared with controls [Fink *et al.* 2006].

Bone loss in men is less rapid than postmenopausal bone loss in women, and occurs primarily by trabecular thinning secondary to reduced formation within each basic multicellular unit as demonstrated by noninvasive high-resolution peripheral quantitative computed tomography scanning. Although women lose trabeculae with an increase in trabecular spacing, men sustain trabecular thinning with no change in trabecular numbers or spacing [Khosla *et al.* 2006]. The preservation of trabecular numbers in men may also help explain their lower lifetime risk of fractures. For men, trabecular bone loss begins early in life, with 42% of trabecular bone being lost before age 50; changes in concentrations of insulin-like growth factor 1 being a possible factor. In contrast, 85% of cortical bone is lost after age 50, being related to subsequent decline in bioavailable sex steroids and increased bone remodelling [Riggs *et al.* 2008].

Secondary causes of bone loss in men

Secondary causes of osteoporosis in men are common and a significant cause of osteoporosis in men (Table 1) [Ebeling, 2008]. Secondary causes need to be excluded in men younger than 50 years when the *Z* score is less than −2 (2 standard deviations below the age-specific mean) on bone densitometry, and in men older than 50 years with osteoporosis. The most common secondary causes are glucocorticoid use, excessive alcohol use, tobacco use and hypogonadism.

Hypogonadism

Hypogonadism occurs in up to 12.3% of men [Mohr *et al.* 2005], and is a significant contributor

Table 1. Secondary causes of osteoporosis.

Common	Cushing's syndrome or exogenous corticosteroid use (>5 mg/day for >3 months)
	Excessive alcohol use (more than two standard drinks per day)
	Primary or secondary hypogonadism
	Inadequate calcium intake (<600 mg/day)
	Vitamin D deficiency/insufficiency
	Tobacco
	Family history
Less common	Low body mass index (<20)
	Lack of exercise or excessive exercise
	Antiepileptic drugs (phenytoin, phenobarbitone, primidone, carbamazepine)
	Thyrotoxicosis
	Primary hyperparathyroidism
	Type 1 and type 2 diabetes mellitus
	Chronic liver or kidney disease
	Malabsorption, including coeliac disease
	Hypercalciuria
	Rheumatoid arthritis or ankylosing spondylosis
Rare	Multiple myeloma
	Human immunodeficiency virus infection or its treatment with protease inhibitors (tenofovir)
	Mastocytosis
	Immunosuppressive therapy (cyclosporin, tacrolimus)
	Osteogenesis imperfect

to osteoporosis due to the role of sex steroids in bone loss. In older male nursing home residents with hip fractures, up to 66% were found to have hypogonadism [Abbasi *et al.* 1995], whereas up to 20% of men with spinal fractures had hypogonadism, with most being asymptomatic. BMD has been shown to be lower in men with hypogonadism [Finkelstein *et al.* 1987; Stoch *et al.* 2001], although bone turnover may be increased. These findings are concordant with the skeletal effects seen with hypogonadism induced by androgen deprivation therapy for prostate cancer, this being associated with decreased BMD, increased bone turnover and a higher fracture risk [Shahinian *et al.* 2005]. In cases of elevated bone turnover markers, testosterone replacement may reduce biochemical markers of bone resorption [Dillon *et al.* 2008; Wang *et al.* 2001]. Similarly, this would provide a justification for the use of bisphosphonate therapy given its mechanism of action and effects on bone resorption and remodelling frequency.

Hypogonadism may be primary or secondary (Table 2). Secondary iatrogenic causes such as androgen deprivation therapy in prostate cancer

management are especially important to identify since, comparable with the skeletal effects of glucocorticoids, bone loss may occur as little as 6 months after commencement of therapy [Ross and Small, 2002]. Furthermore, given that nutrient supplementation alone, with calcium and vitamin D, may be insufficient to prevent bone loss in this setting, some guidelines advocate use of bisphosphonate therapy if the BMD T score is less than or equal to −2.0 in men who have not previously sustained a minimal trauma fracture [Grossmann *et al.* 2011].

Bisphosphonate therapy
Bisphosphonates are a well studied class of antiresorptive drugs that have been approved as a first-line treatment for osteoporosis. They have a high affinity for hydroxyapatite, allowing avid attachment of the drug to bony surfaces and thus incorporation into bone. Once internalized by osteoclasts, amino-bisphosphonates inhibit the action of farnesyl pyrophosphate synthase. This reduces the activity and viability of osteoclasts and ultimately results in reduced bone resorption.

Table 2. Causes of hypogonadism.

Primary hypogonadism	Genetic/chromosomal disorders (Klinefelter's syndrome)
	Anorchia (congenital or postorchidectomy)
	Cryptorchidism
	Chemotherapy (alkylating agents), radiotherapy
	Orchitis (mumps, human immunodeficiency virus, autoimmune)
	Testicular trauma or torsion
	Medications (glucocorticoids, colchicine)
	Alcohol
	Chronic liver or kidney disease, haemochromatosis
Secondary hypogonadism	Idiopathic
	Kallmann syndrome
	Functional
	Excessive exercise, weight change
	Systemic or intercurrent illness
	Structural
	Pituitary or hypothalamic tumour, prolactinoma
	Infiltration (sarcoidosis, haemochromatosis)
	Cranial irradiation, surgery, head trauma
	Medications/iatrogenic
	Androgen deprivation therapy for treatment of prostate cancer
	Opioids
	Exogenous administration of androgens

Oral bisphosphonates have been demonstrated to be effective in fracture reduction in postmenopausal women [Wells *et al.* 2008a, 2008b]. Alendronate is effective for the primary prevention of vertebral fractures and secondary prevention of vertebral, nonvertebral, hip and wrist fractures [Wells *et al.* 2008b]. Similarly, risedronate has a role in secondary prevention of vertebral, nonvertebral and hip fractures [Wells *et al.* 2008a].

In contrast, there are few quality studies with primary fracture outcome data in men, with many utilizing surrogate markers including bone turnover markers and BMD [Boonen *et al.* 2009; Orwoll *et al.* 2000, 2010a, 2010b]. Despite this, the similar antiresorptive effect seen in men, as supported by increases in BMD and reductions in bone resorptive markers, supports the use of bisphosphonates in men. In circumstances of higher bone turnover such as hypogonadism, bisphosphonates may play an even more substantial role.

Alendronate
Numerous studies have demonstrated the efficacy of alendronate in men with osteoporosis. The most recent randomized controlled study reaffirmed the results of numerous previous studies by demonstrating improved BMD and reduced bone turnover markers [Orwoll *et al.* 2010b].

In terms of antifracture efficacy, a randomized double-blind trial in 241 men with hypogonadism or eugonadism showed that alendronate at a dose equivalent to 10 mg per day increased spinal and femoral neck BMD while also reducing the incidence of quantitative, rather than clinical, vertebral fractures at 2 years (0.8% *versus* 7.1% in the placebo arm) [Orwoll *et al.* 2000]. This trial was not powered to assess reductions in other fractures, including hip fractures. A subsequent meta-analysis demonstrated a reduction in vertebral fractures (odds ratio 0.44) [Sawka *et al.* 2005]. However, the reduction in nonvertebral fractures was not statistically significant due to a lack of study power secondary to the small number of nonvertebral fractures in the treatment and placebo groups, and the paucity of nonvertebral fracture data in the assessed trials. Importantly, the use of alendronate in men with primary osteoporosis having a high fracture risk is supported by a cost-effectiveness analysis [Borgstrom *et al.* 2004].

Alendronate has also been shown to be efficacious in men with secondary causes of osteoporosis,
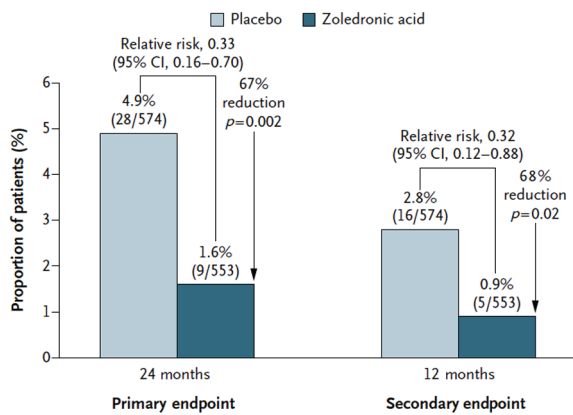
Figure 1. Relative risks of one or more new morphometric vertebral fractures in the modified intention-to-treat population of men with osteoporosis, for zoledronic acid *versus* placebo. Reproduced with permission from Boonen *et al.* [2012].

such as glucocorticoid use and androgen deprivation therapy. Alendronate has been shown to increase the lumbar spine BMD in men with glucocorticoid-induced osteoporosis, with few adverse events [Lespessailles, 2013]. In one clinical trial comparing weekly alendronate 70 mg with placebo, there was a significant increase in BMD at the lumbar spine and hip after 12 months [Stoch *et al.* 2009]. Similarly, weekly alendronate increases lumbar spine BMD compared with placebo in the setting of androgen deprivation therapy [Greenspan *et al.* 2007], while also being cost effective [Ito *et al.* 2010].

Risedronate
Like alendronate, data support the efficacy of risedronate in men with osteoporosis. In one 12-month study, risedronate 5 mg per day given for 12 months increased spinal and proximal femur BMD in men with osteoporosis [Ringe *et al.* 2006]. This open-label study showed a reduction in vertebral fractures, but had the shortcoming of not being blinded.

A more recent randomized clinical trial of 284 men with osteoporosis compared weekly risedronate 35 mg with placebo, reported that risedronate increased lumbar spine BMD [Boonen *et al.* 2009]. Importantly, there was no reduction in incident fractures with risedronate as these occurred infrequently and the study was not powered to detect improvements in fracture endpoints. Therefore, more data are required to determine the antifracture efficacy of oral

bisphosphonates, including risedronate, particularly regarding nonvertebral and hip fractures.

Intravenous bisphosphonates
Intravenous bisphosphonates, such as zoledronic acid, present an alternative option to oral bisphosphonates, avoiding gastrointestinal adverse effects and offering regimens with less frequent dosing and thus improving adherence to therapy. Potential adverse effects include an acute phase reaction with fever and myalgia after the first infusion, worsening of renal impairment and, rarely, jaw osteonecrosis [Bilezikian, 2006]. While monthly ibandronate has been shown to improve BMD and bone turnover markers [Orwoll *et al.* 2010a], zoledronic acid is the better studied of the intravenous bisphosphonates in terms of antifracture efficacy.

In one randomized trial, zoledronic acid at an annual dose of 5 mg reduced overall clinical fractures (35% relative risk reduction) and mortality, but not hip fractures, in older men and women over a 1.9-year follow-up period after hip fracture [Lyles *et al.* 2007]. Furthermore, zoledronic acid reduced mortality by 28% compared with placebo ($p = 0.02$).

A recent comparative study of once-yearly zoledronic acid 5 mg and once-weekly alendronate demonstrated noninferiority of zoledronic acid with regards to changes in BMD and bone turnover markers in men with osteoporosis [Orwoll *et al.* 2010b]. Zoledronic acid increased lumbar spine BMD at 24 months by 6.1% while bone turnover markers at 12 months were comparable in both treatment arms. Adverse event rates were similar and, although few in number, incident vertebral fracture rates were similar in both groups. Significantly, based on questionnaire responses, most men preferred the once-yearly zoledronic acid infusion (74.2%) compared with alendronate.

The most recently published multicentre double-blind, placebo-controlled trial of 1199 men reported fewer incident vertebral fractures with zoledronic acid (1.6% *versus* 4.9%, $p = 0.002$), along with significant increases in BMD and decreases in bone turnover markers (Figure 1) [Boonen *et al.* 2012]. Compared with men who received placebo, men who received zoledronic acid also had fewer moderate to severe vertebral fractures and less height loss. Although this study supports the antifracture efficacy for zoledronic

acid in men with eugonadism and hypogonadism, overall there remains a lack of data demonstrating antifracture efficacy for nonvertebral and hip fractures in men; most studies had few such fractures and thus were underpowered to assess the effects on these clinical endpoints.

In the setting of androgen deprivation therapy for prostate cancer, there is also evidence supporting the use of intravenous bisphosphonates. Pamidronate has been shown to prevent the initial bone loss seen following initiation of androgen deprivation therapy [Smith *et al.* 2001], whereas zoledronic acid increased lumbar spine BMD by 5.6% at 1 year compared with a decrease of 2.2% with placebo [Smith *et al.* 2003]. However, both studies were underpowered to assess antifracture efficacy.

Alternative and adjunctive therapies

Denosumab

Denosumab, a fully human monoclonal antibody that specifically targets receptor activator of nuclear factor κB ligand, is a potential alternative antiresorptive agent to bisphosphonate therapy. Similarly, its effectiveness in the prevention of bone loss in the setting of androgen deprivation therapy for nonmetastatic prostate cancer has been demonstrated [Smith *et al.* 2009]. In addition to improvements in BMD, the incidence of new vertebral fractures was decreased over three years. However, there were no significant reductions in nonvertebral or hip fractures.

Teriparatide

Anabolic agents, such as teriparatide, may remedy an underlying defect in osteoblast function, which has been implicated in men with idiopathic osteoporosis [Orwoll and Klein, 1995; Rosen and Bilezikian, 2001]. Studies show teriparatide or PTH(1-34) increases spinal and proximal femur BMD in men with hypogonadism or eugonadism and osteoporosis [Orwoll *et al.* 2003]. In follow-up studies, prior teriparatide therapy significantly reduced moderate and severe vertebral fractures, and nonvertebral while data on nonvertebral or hip fractures in men are lacking [Kaufman *et al.* 2005].

Despite the purported complementary actions of bisphosphonates and teriparatide on osteoclasts and osteoblasts respectively, the addition of alendronate to teriparatide blunts the increase in

BMD stimulated by teriparatide in men [Finkelstein *et al.* 2003]. Antecedent treatment with risedronate compared with alendronate led to greater increases in bone formation markers and BMD [Miller *et al.* 2008]. Notwithstanding, bisphosphonates continue to play a significant role in men who receive teriparatide for severe osteoporosis since their commencement after cessation of teriparatide is mandatory and instigates further gains in BMD [Kurland *et al.* 2004].

Testosterone

Studies of testosterone in men with osteoporosis are limited and none have used fractures as a primary endpoint. In men with hypogonadism, testosterone therapy has a comparable effect with bisphosphonate therapy, with improvements in bone turnover markers and BMD [Katznelson *et al.* 1996; van der Werff ten Bosch and Bot, 1992]. In a 2-year observational study, microscopic magnetic resonance imaging parameters of trabecular connectivity improved, suggesting testosterone may improve trabecular architecture in men with hypogonadism [Benito *et al.* 2005]. The effects of testosterone therapy in men with eugonadism remain uncertain.

Although there are no studies investigating the combination of testosterone and bisphosphonates and despite both having similar effects on bone turnover and density, there remains a justification for bisphosphonate use in men receiving sex steroids to restore eugonadism. As previously discussed, bisphosphonate therapy is effective in men with hypogonadism and eugonadism, with studies demonstrating antifracture efficacy. Therefore, in addition to bisphosphonate therapy, eugonadal status should be restored in men without contraindications to sex hormone replacement through adjunctive testosterone therapy in those with high fracture risk.

Conclusion

Despite the relative paucity of studies investigating the use of bisphosphonates in men with osteoporosis, particularly with respect to antifracture efficacy, both oral and intravenous bisphosphonates have positive effects on surrogate markers, including bone turnover markers and bone density. Furthermore, despite the lack of data on efficacy on hip and nonvertebral fractures recent studies confirm the benefit of both oral and intravenous bisphosphonate therapy in reducing vertebral

fractures in men with osteoporosis. Bisphosphonates have a role as monotherapy, as consolidative therapy after a course of teriparatide therapy or in combination with testosterone replacement in men at high risk of fracture with hypogonadism.

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Conflict of interest statement

References

Abbasi, A., Rudman, D., Wilson, C., Drinka, P., Basu, S., Mattson, D. *et al.* (1995) Observations on nursing home residents with a history of hip fracture. *Am J Med Sci* 310: 229–234.

Benito, M., Vasilic, B., Wehrli, F., Bunker, B., Wald, M., Gomberg, B. *et al.* (2005) Effect of testosterone replacement on trabecular architecture in hypogonadal men. *J Bone Miner Res* 20: 1785–1791.

Bilezikian, J. (2006) Osteonecrosis of the jaw – do bisphosphonates pose a risk? *N Engl J Med* 355: 2278–2281.

Boonen, S., Orwoll, E., Wenderoth, D., Stoner, K., Eusebio, R. and Delmas, P. (2009) Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. *J Bone Miner Res* 24: 719–725.

Boonen, S., Reginster, J., Kaufman, J., Lippuner, K., Zanchetta, J., Langdahl, B. *et al.* (2012) Fracture risk and zoledronic acid therapy in men with osteoporosis. *N Engl J Med* 367: 1714–1723.

Borgstrom, F., Johnell, O., Jonsson, B., Zethraeus, N. and Sen, S. (2004) Cost effectiveness of alendronate for the treatment of male osteoporosis in Sweden. *Bone* 34: 1064–1071.

Chang, K., Center, J., Nguyen, T. and Eisman, J. (2004) Incidence of hip and other osteoporotic fractures in elderly men and women: Dubbo Osteoporosis Epidemiology Study. *J Bone Miner Res* 19: 532–536.

Cooper, C., Atkinson, E., O'Fallon, W. and Melton, L., 3rd (1992) Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. *J Bone Miner Res* 7: 221–227.

Dillon, E., Urban, R., Angel, J., Casperson, S., Paddon-Jones, D. and Sheffield-Moore, M. (2008) Continuous testosterone administration for 5 months reduces markers of bone turnover in older men. *FASEB J* 22: 1188.

Ebeling, P. (1998) Osteoporosis in men. New insights into aetiology, pathogenesis, prevention and management. *Drugs Aging* 13: 421–434.

Ebeling, P.R. (2012) Clinical practice. Osteoporosis in men. *New Engl J Med* 358(14):1474–82.

Fink, H., Ewing, S., Ensrud, K., Barrett-Connor, E., Taylor, B., Cauley, J. *et al.* (2006) Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. *J Clin Endocrinol Metab* 91: 3908–3915.

Finkelstein, J., Hayes, A., Hunzelman, J., Wyland, J., Lee, H. and Neer, R. (2003) The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 349: 1216–1226.

Finkelstein, J., Klibanski, A., Neer, R., Greenspan, S., Rosenthal, D. and Crowley, W., Jr, (1987) Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. *Ann Intern Med* 106: 354–361.

Greenspan, S., Nelson, J., Trump, D. and Resnick, N. (2007) Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med* 146: 416–424.

Grossmann, M., Hamilton, E., Gilfillan, C., Bolton, D., Joon, D. and Zajac, J. (2011) Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. *Med J Aust* 194: 301–306.

Gullberg, B., Johnell, O. and Kanis, J. (1997) World-wide projections for hip fracture. *Osteoporos Int* 7: 407–413.

Ito, K., Elkin, E., Girotra, M. and Morris, M. (2010) Cost-effectiveness of fracture prevention in men who receive androgen deprivation therapy for localized prostate cancer. *Ann Intern Med* 152: 621–629.

Jones, G., Nguyen, T., Sambrook, P., Kelly, P. and Eisman, J. (1994) Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. *BMJ* 309: 691–695.

Jones, G., White, C., Nguyen, T., Sambrook, P., Kelly, P. and Eisman, J. (1996) Prevalent vertebral deformities: relationship to bone mineral density and spinal osteophytosis in elderly men and women. *Osteoporos Int* 6: 233–239.

Katznelson, L., Finkelstein, J., Schoenfeld, D., Rosenthal, D., Anderson, E. and Klibanski, A. (1996)

Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab* 81: 4358–4365.

Kaufman, J., Orwoll, E., Goemaere, S., San Martin, J., Hossain, A., Dalsky, G. *et al.* (2005) Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporos Int* 16: 510–516.

Khosla, S., Lufkin, E., Hodgson, S., Fitzpatrick, L. and Melton, L., 3rd (1994) Epidemiology and clinical features of osteoporosis in young individuals. *Bone* 15: 551–555.

Khosla, S., Riggs, B., Atkinson, E., Oberg, A., McDaniel, L., Holets, M. *et al.* (2006) Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. *J Bone Miner Res* 21: 124–131.

Krabbe, S., Hummer, L. and Christiansen, C. (1984) Longitudinal study of calcium metabolism in male puberty. II. Relationship between mineralization and serum testosterone. *Acta Paediatr Scand* 73: 750–755.

Kurland, E., Heller, S., Diamond, B., McMahon, D., Cosman, F. and Bilezikian, J. (2004) The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide [human parathyroid hormone(1-34)]. *Osteoporos Int* 15: 992–997.

Lespessailles, E. (2013) Bisphosphonates and glucocorticoid-induced osteoporosis: efficacy and tolerability. *Joint Bone Spine* 80: 258–264.

Lyles, K., Colon-Emeric, C., Magaziner, J., Adachi, J., Pieper, C., Mautalen, C. *et al.* (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 357: 1799–1809.

Miller, P., Delmas, P., Lindsay, R., Watts, N., Luckey, M., Adachi, J. *et al.* (2008) Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. *J Clin Endocrinol Metab* 93: 3785–3793.

Mohr, B., Guay, A., O'Donnell, A. and McKinlay, J. (2005) Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. *Clin Endocrinol (Oxf)* 62: 64–73.

Morishima, A., Grumbach, M., Simpson, E., Fisher, C. and Qin, K. (1995) Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab* 80: 3689–3698.

Nguyen, T., Eisman, J., Kelly, P. and Sambrook, P. (1996) Risk factors for osteoporotic fractures in elderly men. *Am J Epidemiol* 144: 255–263.

Nordstrom, P., Neovius, M. and Nordstrom, A. (2007) Early and rapid bone mineral density loss of the proximal femur in men. *J Clin Endocrinol Metab* 92: 1902–1908.

O'Neill, T., Felsenberg, D., Varlow, J., Cooper, C., Kanis, J. and Silman, A. (1996) The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. *J Bone Miner Res* 11: 1010–1018.

Orwoll, E., Binkley, N., Lewiecki, E., Gruntmanis, U., Fries, M. and Dasic, G. (2010a) Efficacy and safety of monthly ibandronate in men with low bone density. *Bone* 46: 970–976.

Orwoll, E., Ettinger, M., Weiss, S., Miller, P., Kendler, D., Graham, J. *et al.* (2000) Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 343: 604–610.

Orwoll, E. and Klein, R. (1995) Osteoporosis in men. *Endocr Rev* 16: 87–116.

Orwoll, E., Miller, P., Adachi, J., Brown, J., Adler, R., Kendler, D. *et al.* (2010b) Efficacy and safety of a once-yearly i.v. Infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. *J Bone Miner Res* 25: 2239–2250.

Orwoll, E., Scheele, W., Paul, S., Adami, S., Syversen, U., Diez-Perez, A. *et al.* (2003) The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 18: 9–17.

Pietschmann, P., Kudlacek, S., Grisar, J., Spitzauer, S., Woloszczuk, W., Willvonseder, R. *et al.* (2001) Bone turnover markers and sex hormones in men with idiopathic osteoporosis. *Eur J Clin Invest* 31: 444–451.

Riggs, B., Melton, L., Robb, R., Camp, J., Atkinson, E., McDaniel, L. *et al.* (2008) A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. *J Bone Miner Res* 23: 205–214.

Ringe, J., Faber, H., Farahmand, P. and Dorst, A. (2006) Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. *Rheumatol Int* 26: 427–431.

Rosen, C. and Bilezikian, J. (2001) Clinical review 123: Anabolic therapy for osteoporosis. *J Clin Endocrinol Metab* 86: 957–964.

Ross, R. and Small, E. (2002) Osteoporosis in men treated with androgen deprivation therapy for prostate cancer. *J Urol* 167: 1952–1956.

Sawka, A., Papaioannou, A., Adachi, J., Gafni, A., Hanley, D. and Thabane, L. (2005) Does alendronate reduce the risk of fracture in men? A meta-analysis incorporating prior knowledge of anti-fracture efficacy in women. *BMC Musculoskelet Disord* 6: 39.

Seeman, E., Bianchi, G., Khosla, S., Kanis, J. and Orwoll, E. (2006) Bone fragility in men – where are we? *Osteoporos Int* 17: 1577–1583.

Shahinian, V., Kuo, Y., Freeman, J. and Goodwin, J. (2005) Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 352: 154–164.

Smith, E., Boyd, J., Frank, G., Takahashi, H., Cohen, R., Specker, B. *et al.* (1994) Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med* 331: 1056–1061.

Smith, M., Eastham, J., Gleason, D., Shasha, D., Tchekmedyian, S. and Zinner, N. (2003) Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 169: 2008–2012.

Smith, M., Egerdie, B., Hernandez Toriz, N., Feldman, R., Tammela, T., Saad, F. *et al.* (2009) Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 361: 745–755.

Smith, M., McGovern, F., Zietman, A., Fallon, M., Hayden, D., Schoenfeld, D. *et al.* (2001) Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 345: 948–955.

Stoch, S., Parker, R., Chen, L., Bubley, G., Ko, Y., Vincelette, A. *et al.* (2001) Bone loss in men with prostate cancer treated with gonadotropin-releasing hormone agonists. *J Clin Endocrinol Metab* 86: 2787–2791.

Stoch, S., Saag, K., Greenwald, M., Sebba, A., Cohen, S., Verbruggen, N. *et al.* (2009) Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. *J Rheumatol* 36: 1705–1714.

Szulc, P. and Delmas, P. (2001) Biochemical markers of bone turnover in men. *Calcif Tissue Int* 69: 229–234.

van der Werff ten Bosch, J. and Bot, A. (1992) Some skeletal dimensions of males with isolated gonadotrophin deficiency. *Neth J Med* 41: 259–263.

Wang, C., Swerdloff, R., Iranmanesh, A., Dobs, A., Snyder, P., Cunningham, G. *et al.* (2001) Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf)* 54: 739–750.

Wells, G., Cranney, A., Peterson, J., Boucher, M., Shea, B., Robinson, V. *et al.* (2008a) Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* (1): CD004523.

Wells, G., Cranney, A., Peterson, J., Boucher, M., Shea, B., Robinson, V. *et al.* (2008b) Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* (1): CD001155.

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