Osteoporosis is a disease characterized by low bone mass and deterioration in the microarchitecture of bone tissue, leading to an increased risk of fracture. Osteoporosis occurs when the bone mass decreases more quickly than the body can replace it, leading to a net loss of bone strength. As a result the skeleton becomes fragile, so that even a slight bump or fall can lead to a broken bone, (referred to as a fragility fracture). Osteoporosis has no signs or symptoms until a fracture occurs – this is why it is often called a ‘silent disease’.

Osteoporosis affects all bones in the body; however, fractures occur most frequently in the vertebrae (spine), wrist and hip. Osteoporotic fractures of the pelvis, upper arm and lower leg are also common. Osteoporosis itself is not painful but the broken bones can result in severe pain, significant disability and even mortality. Both hip and spine fractures are also associated with a higher risk of death - 20% of those who suffer a hip fracture die within 6 months after the fracture.

A COMMON DISEASE

It is estimated that worldwide an osteoporotic fracture occurs every three seconds. At 50 years of age, one in three women and one in five men will suffer a fracture in their remaining lifetime. For women, the risk of hip fracture is higher than the risk of breast, ovarian and uterine cancer combined. For men, the risk is higher than the risk for prostate cancer.

Approximately 50% of people with one osteoporotic fracture will have another, with the risk of new fractures rising exponentially with each fracture.

A GROWING PUBLIC HEALTH PROBLEM

The risk of sustaining a fracture increases exponentially with age due not only to the decrease in bone mineral density, but also due to the increased rate of falls among the elderly. The elderly represent the fastest growing segment of the population. Thus, as life expectancy increases for the majority of the world’s population, the financial and human costs associated with osteoporotic fractures will increase dramatically unless preventive action is taken.
One-third of hip fractures worldwide occur in men and they are associated with greater mortality when compared with women.

This statistic is remarkable because hip fractures represent the most serious complication of osteoporosis, a disease that for far too long has been considered to be exclusively a problem for women. While improving management of osteoporosis for women is critical, the time has now come for a radical reappraisal of osteoporosis management in men.

The world’s men are ageing fast; by 2050 the number of men aged 60 years or over will increase 10-fold. As male baby boomers enter old age, the number of men living with osteoporosis and the associated suffering from consequent fragility fractures is set to escalate to an unprecedented level.

Although all of the world’s regions will be affected, Asia and Latin America will bear the brunt of increased demand for acute fracture care services because of the growth in their ageing populations over the next 30 years. Given that 3.5 million fragility fractures occurred in men in 2000, the costs that will result from the projected increases in male fracture incidence will place an unbearable strain on overstretched health-care budgets.

To avert this calamity, a concerted international effort is required to improve the awareness of osteoporosis in men amongst both doctors and the community, and to implement systems of care to prevent fragility fractures. In this regard, there is good news. There are a range of therapies now available that have proven effective in the treatment of osteoporosis in men. These treatments have been shown to work against the various types of osteoporosis which can affect men, including primary (or idiopathic) osteoporosis and when secondary causes are responsible for bone loss (e.g. glucocorticoids or low sex hormone levels).

The key challenge facing health-care professionals and policymakers is to ensure that men who are clearly at high risk of suffering fragility fractures get the care they need. First and foremost, this includes men who have already suffered a fragility fracture. A broken bone is a very clear signal of elevated future fracture risk – nevertheless osteoporosis assessment and treatment rates among these men are very low – being mostly under 20%. Studies from around the world, reviewed in this report, demonstrate a near universal absence of secondary fracture prevention systems for men who have already suffered fragility fractures. Similar poor attention to bone health is evident among men receiving androgen deprivation therapy for prostate cancer or glucocorticoid treatment for many other conditions, the most common causes of secondary osteoporosis in men.

A systematic approach to osteoporosis management in men is required on a global scale, including the implementation of awareness and educational programmes as well as Fracture Liaison Services (FLS), which are proven systems of care for patients who suffer fragility fractures. FLS place a fracture coordinator at its centre and can result in fewer fractures, cost savings for the health system and improvement in the quality of life of patients. FLS is the focus of the International Osteoporosis Foundation’s (IOF) Capture the Fracture Campaign. A growing number of centres of excellence are sharing their experience with colleagues elsewhere to catalyse the establishment of FLS in many countries. Governments are recognizing the need to incorporate FLS into national policy. Closure of the evidence-treatment gap for men with fragility fractures or men who have been initiated on bone-thinning treatments for other diseases can be achieved so easily. Development of robust protocols and systems of care to deliver them – which ensure a bone-health assessment goes hand-in-hand with the presence of a fragility fracture or upon initiation of bone-thinning drugs – will transform osteoporosis care for men.

Policymakers must not discriminate against men by their omission from national clinical guidelines and reimbursement policies. Governments and health-care professionals the world over must ask themselves whether this is an issue inhibiting optimal osteoporosis care for men in their jurisdictions. Where change is needed, it must happen now.

The demographic tsunami of ageing is upon us. Elimination of the osteoporosis evidence-treatment gap for men is an essential component of our response to this unprecedented threat to the sustainability of our health-care systems.
In 1950, there were approximately 90 million men in the world aged 60 years or over. By the turn of the century, there were almost 275 million and by 2050 there will be more than 900 million men who have lived into their seventh decade (Figure 1). This 10-fold increase in the older male population in just a century is a longevity miracle. However, a demographic shift on this scale creates challenges which – with absolute certainty – will include an explosion in the incidence of chronic diseases afflicting older men. These diseases will not only impose a great burden upon men and their families but they will also test our health and social care systems to the limit. Osteoporosis will be at the vanguard of this battle set to rage between quantity and quality of life.

All too often, osteoporosis is perceived to be a ‘woman’s disease’ that is not preventable or an urgent health concern to men. The primary purpose of this report is to debunk these myths and raise awareness of the threat that osteoporosis poses to older men throughout the world. It is estimated that the residual lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 is up to 27% higher than the lifetime risk of developing prostate cancer of 11.3%.

And just as osteoporosis does not discriminate between the sexes – with
Osteoporotic fractures affecting one in five men versus one in three women aged over 50 years – its impact will be felt in the coming decades in the majority of the world’s regions. As illustrated in Figure 2, the population of men aged over 60 years who are potentially at risk of suffering fragility fractures will continue to grow in Europe, Northern America and Oceania, whilst in Asia and Latin America the rate of growth of the male population aged 60 years or over will be exponential.

FIGURE 2 Proportion of men aged ≥60 years by world region 1950–2050

Osteoporosis causes fragility fractures, which are fractures that usually result from a fall from a standing height or less. Arguably, the most serious fragility fracture is a hip fracture, and one-third of all hip fractures worldwide occur in men. Audits from several countries have shown that a significant proportion of men who suffer hip fractures have broken other bones before they broke their hip. Furthermore, a study from Sweden, which followed a cohort of older men for 22 years, reported that 27% of men who had suffered a hip fracture sustained subsequent fractures in their remaining lifetime. When men suffer fractures caused by osteoporosis – like women – too many become trapped in the fragility fracture cycle.

For older working men, fragility fractures have been demonstrated to have a significant impact on productivity. In Denmark, a national evaluation of the impact of fragility fractures concluded that almost 5,000 working days would be lost on account of fractures in men aged 50–65 years. A recently published burden of disease analysis from Osteoporosis Australia concluded that productivity losses among Australian men aged 50 years or over with fragility fractures cost more than 46 million AUD in 2012.

In terms of mortality related to fragility fractures, men fare particularly badly and are the ‘weaker sex’. A national registry study from Denmark published in 2010 echoed the findings of previous studies: Hip fractures in men are associated with greater mortality compared with women, with rates as high as 37% in the first year following fracture. In addition, mortality is increased after most fragility fractures in men, not only following hip fractures.

In recent years, substantial geographic variation in the incidence of hip and other fragility fractures has been observed. In general, hip fracture rates appear to be increasing rapidly in the East whilst age-adjusted rates for women have stabilized, or declined, in the West. This decline in age-adjusted rates of hip fractures in the West has been less marked amongst men. Notably, a growing number of studies have reported large increases in the absolute incidence of hip fracture in men during short intervals of time. A recent study from the UK of more than 10,000 hip fracture admissions to a major trauma centre noted a substantial increase in the proportion of hip fractures occurring in men in a 12-year period. In 2000, 23.5% of the hip fractures occurred in men, which increased to 30.7% by 2012.

Hip fractures in men are associated with greater mortality compared with women, with rates as high as 37% in the first year following fracture. In addition, mortality is increased after most fragility fractures in men, not only following hip fractures.
The following summary illustrates the current burden that osteoporosis imposes on the world’s men, and gives an indication of how that burden will grow in the coming decades in different regions.

In the year 2000, the worldwide prevalence of fragility fractures in men was estimated at:
- 490,000 hip fractures (30.1% of all hip cases)
- 554,000 vertebral fractures (39.1% of all vertebral cases)
- 3.5 million fragility fractures (38.7% of all fragility fractures)

In a 2013 IOF report reviewing the management, epidemiology and burden of osteoporosis in the European Union, it was estimated that in 2010
- 5.5 million men had osteoporosis and almost 1.2 million had suffered fragility fractures.

More than 168,000 hip fractures occurred in men, representing 28% of the total number of hip fractures in both sexes. Sixty-five per cent of these fractures occurred in just five countries (Figure 3: Germany, UK, Italy, France and Spain).

The number of men aged 50 years or over in 2010 that had suffered a hip or vertebral fracture in previous years, was 895,000 and 1,040,000, respectively. More than 20,100 men died directly as a result of their fracture – within 12 months of it occurring – and more than 12,000 life-years were lost. The cost burden imposed, excluding the value of quality adjusted life years (QALYs) lost, was almost 11.6 billion EUR. Projections suggest that the total number of fractures will increase by 34% by 2025, to almost 1.6 million cases per year, with an attendant cost of 15.5 billion EUR.

During 2007–2008, 16,855 Canadian men were hospitalized with a fracture, including almost 8,200 hip fractures. The total cost of treating and rehabilitating fractures in men was 570 million CAD. If the costs of admissions to long-term care facilities were taken into account, the overall annual cost would rise to 910 million CAD.

In the United States, almost 595,000 fractures occurred among men aged 50 years or over in 2005, including almost 74,000 hip fractures. The total cost of treating and rehabilitating fractures in men, including long-term care costs, was 4.1 billion USD. Projections of fracture incidence in 2025 suggest costs will increase to 6.8 billion USD. Another study from the United States highlights that from 2010–2030, the number of hip fractures among men is expected to increase by 51.8% while the number among women is expected to decrease by 3.5%. Whereas men sustained 27.9% of hip fractures in 2010, by 2030 this proportion is expected to rise to 37.8%.
In Argentina, 9,444 hip fractures were estimated to have occurred in men in 2009 at a total cost of 35.9 million USD. By 2050, projections suggest the incidence of hip fractures in men will increase to 13,000 cases per year.

In Brazil, the prevalence of osteoporosis at the femoral neck among men aged 50 years or over has been reported as 15.4%. The Brazilian Osteoporosis Study (BRAZOS) found the prevalence of fragility fracture among men aged 40 years and over to be 12.8%. The number of men suffering hip fractures every year is estimated to be 24,200.

In Mexico, it is estimated that almost 7,800 hip fractures occurred in men in 2009, at a cost of 39 million USD. Hip fracture incidence is projected to increase to 11,700 and 35,500 cases per year by 2020 and 2050, respectively. Among men aged 50 years and over, the prevalence of radiographically detected vertebral fractures is almost 10%.

In 2011, IOF published the Eastern European and Central Asian Regional Audit. This report identified a paucity of epidemiological data on osteoporosis and fragility fractures across the region. Another finding was surprisingly low levels of hospitalization and surgery for hip fracture sufferers. In the Russian Federation, between 33–40% of hip fracture sufferers were hospitalized and just 13% received surgical treatment. Consequently, mortality rates for hip fracture in some Russian cities are very high at 45–52%.

In 2012, epidemiological modelling was published for the Russian Federation. More than 142,000 fragility fractures were estimated to have occurred in men in 2010, including more than 32,000 hip fractures. By 2035, projections suggest the number of fragility fractures and hip fractures will increase to more than 177,000 and almost 43,700, respectively.

Osteoporosis Australia recently published a new burden of disease analysis for the period 2012–2022. It showed that in 2012, almost 202,000 Australian men aged 50 years or over had osteoporosis and more than 40,700 suffered a fragility fracture, including 6,670 hip fractures. Other key findings related to men included:

- The total cost of hip fractures in men in 2012 was almost 188 million AUD (28,177 AUD per case) comprised of:
  - Total hospital costs: 144,634,902 AUD
  - Pre-hospital ambulance/paramedic costs: 4,592,466 AUD
  - Sub-acute care (i.e. rehabilitation) costs: 20,215,518 AUD
  - Community costs for fracture management: 773,009 AUD
  - Nursing home care costs: 17,724,884 AUD

- The total cost of all fragility fractures in men in 2012 was almost 426 million AUD. By 2022, older men will suffer more than 55,300 fractures, including 10,000 hip fractures.

In China, as the enormous Chinese population simultaneously ages and urbanizes, fracture incidence is changing dramatically. In Beijing, from 2002–2006, hip fracture rates in men aged 50 years or over increased by 49%. In Tangshan in Hebei province, from 1994–2010, hip fracture rates in men aged 70 years or over increased by 85%.

In Japan, hip fracture incidence has been reported in a nationwide survey conducted every five years since 1987. The number of hip fractures occurring annually in men rose from 13,500 cases in 1987 to 31,300 in 2007.

In Saudi Arabia, estimates suggest that almost 8,800 hip fractures occurred in men and women combined during 2004. With a notably high observed male to female ratio of 1.2:1, approximately 4,800 hip fractures occur annually in Saudi men. The total cost of managing hip fractures in men was estimated at 622 million USD.

In Turkey, almost 6,500 men were estimated to have suffered a hip fracture in 2010. By 2035, projections suggest that each year 14,860 men will break their hip. The remaining lifetime risk of hip fracture for a 50 year old Turkish man is 3.5%.

In Iran, almost 22,000 hip fractures occurred in men in 2010, a figure which is expected to increase to almost 29,000 by 2020 and 43,500 by 2050 (B. Larijani, personal communication, July 21, 2014).
Many factors influence the growth of our skeleton and maintenance of its bone mass throughout life. As illustrated in Figure 4, both males and females attain peak bone mass between ages 20–30 years. Up to the age of 10–12 years, there are no significant differences in bone mass between boys and girls. However, at the onset of puberty, the bone mass increases more in males. Why does this occur? Accrual of bone mass during childhood and adolescence is controlled by sex steroids and the growth hormone/insulin-like growth factor 1 (IGF-I) axis of the endocrine system. A study of young men from Gothenburg sought to establish whether androgens increase the size of cortical bone — the hard ‘outer casing’ of bones — and whether oestrogens have the opposite effect. Levels of free testosterone and oestradiol were measured and correlated with the size of cortical bone. The results supported the notion that androgens increase, whereas oestrogens reduce, cortical bone size. Consequently, during puberty, boys develop larger bones than girls and so accrue greater bone mass. The size of bones and the thickness of their cortex are major determinants of bone strength, and thus men generally

![FIGURE 4 Bone mass throughout the life cycle](image)
have larger bone size and greater bone strength than women.

Achieving one’s genetic potential for peak bone mass during childhood and adolescence is the primary objective during this first stage of the skeleton’s life cycle. The consequence of not doing so has been illustrated by computer modelling developed to predict the relative influences of peak bone mineral density (BMD), menopause and age-related bone loss on the development of osteoporosis in women. A 10% increase in peak BMD was predicted to delay the development of osteoporosis by 13 years. Important influences on peak bone mass for young males include:

**Exercise** Osteoporosis Australia’s Building healthy bones throughout life strategy published in 2013 stated ‘Childhood and adolescence may represent the optimal window of opportunity in which exercise can improve bone strength and protect against osteoporosis and associated fragility fractures in old age, assuming the gains achieved are maintained in later life.’ Systematic literature review has reported beneficial effects on BMD for children participating in moderate to high impact weight-bearing physical activities. Long-term follow-up from the Australian Schools Health and Fitness Survey conducted in 1985 suggests that higher levels of fitness as a child are predictive of greater peak bone mass at age 30 years.

**Calcium intake** approximately 40% of adult peak bone mass is acquired during the two years around puberty. Accordingly, ensuring adequate dietary calcium intake during this period of growth is essential. In this regard, it is of great concern that a multinational study of calcium intakes in adolescent boys reported levels of only 60% of country-specific requirements.

**Vitamin D levels** the association between vitamin D deficiency and rickets is well documented and understood. However, the impact that vitamin D deficiency in childhood has on bone health at the population level is also likely to be significant. Reports from Europe, the Middle East, South America and Oceania suggest low levels of vitamin D in children are a cause for concern throughout the world. In 2011, the Institutes of Medicine report on dietary intakes of vitamin D and calcium defined the adequate intake of vitamin D of infants (0–12 months old) to be 400 IU and the recommended dietary allowance of vitamin D for children aged 1–18 years to be 600 IU/day.

**Protein intake** proteins are building blocks and help to maintain strong bones, conversely low protein intake is associated with impaired skeletal growth thereby influencing peak bone mass. Proteins may have a positive effect on bone and muscle through hepatic production of insulin-like growth factor I (IGF-I). Serum levels of IGF-I are closely related to growth, increasing from birth to puberty. Furthermore IGF-I is considered as a major factor for bone longitudinal growth, stimulating chondrocyte from the growth plate and stimulating the production of active form of vitamin D (1,25 dihydroxyvitamin D) in the kidney. Dairy products, fish, meat, nuts and legumes are a good dietary source of proteins. Both animal and plant proteins sources appear to favour strong bones. Other factors which can adversely affect peak bone mass and BMD in young males include delayed puberty, smoking, alcohol consumption and certain childhood diseases such as acute lymphoblastic leukaemia and medications such as glucocorticoids and anti-epileptic drugs.

**AGES 20–60 YEARS**

During these decades of adulthood, the primary objective is to avoid premature bone loss and maintain a healthy skeleton. On account of the muscular system being the generator of the strongest mechanical forces...
applied to bones, avoiding loss of muscle mass – known as sarcopenia – is also of paramount importance in this stage of life. Accordingly, as for younger males, regular exercise has an important role to play. Recommendations for building healthy bones in healthy adults from Osteoporosis Australia and others provide an illustration of the type and frequency of activities that current knowledge suggests will be of benefit:

- Encourage regular participation in moderate impact weight-bearing physical activity, high impact training (e.g. 50–100 jumps) or related impact loading sports for at least 30 minutes 3–5 days per week.

- Include muscle-strengthening exercises on at least 2 days per week. For maximum benefits, the programme should be high intensity (60–80% of peak capacity), become progressively more challenging over time and target the major muscles around the hip and spine.

- Where possible, encourage participation in a multi-modal exercise regimen (inclusive of weight bearing/high impact/high intensity resistance exercise) at least three times per week.

With regard to calcium intake and vitamin D levels, men should aim to comply with the relevant national recommendations from agencies within their respective countries.

As suggested in Figure 4, bone loss appears to commence soon after young men reach peak bone mass. A study from Sweden investigated changes in BMD in men aged between 17–26 years. A significant year-on-year loss of BMD at the hip was observed from age 19 years, when peak bone mass had occurred. Analysis of bone density data from these young men’s fathers suggested that 25% of BMD at the hip may be lost by 50 years of age and that bone remodelling may be regulated differently at the hip than at other sites.

There are important differences between the ways in which bone loss occurs with ageing in men as compared with women. To appreciate these differences, the basics of bone biology must be firstly considered.

Bone is a living tissue able to impart tremendous strength to support our bodies, yet simultaneously must also have the capacity to be flexible to absorb shock without breaking. As illustrated in Figure 5, bone comes in two major forms, the cortical bone, which forms the casing or outer shell, and the trabecular bone – also known as spongy or cancellous bone – which forms a honeycomb-type mesh within the cortex. The trabecular bone provides structural support when loads are applied and enables the entire bone to be flexible.

Bone is in a perpetual state of remodelling throughout life, with the entire skeleton being replaced every 10 years. One group of cells – osteoclasts – are drawn to sites of microdamage to remove old bone (bone resorption). Once the osteoclasts have completed their task, bone forming cells – osteoblasts – deposit new bone to fill the gap created. This process is known as the bone remodelling cycle and is represented in Figure 6 for a healthy young adult. For bone mass to remain constant, the amount of bone being resorbed by the osteoclasts needs to be equivalent to the amount of bone being formed by the osteoblasts.

As men age, the rate of bone resorption by osteoclasts on the inside surface of cortical bone increases (known as endocortical resorption). At the same time, new bone is being deposited on the outer surface of the cortex (known as periosteal apposition). These concurrent processes lead to an increase in the circumference of bones, which serves to increase the bone size and moves the cortex further away from the centre of the bone. From a biomechanical perspective, both of these changes result in greater bone strength. However, the cortex also becomes thinner which reduces bone strength. So, in men aged younger than 70 years, there is a degree of balance between these two competing processes.

In postmenopausal women, there is evidence to suggest that the rate of endocortical resorption is such that periosteal apposition cannot serve as a sufficient compensatory mechanism to prevent bone fragility. The change
in cross-sectional structure of bone for men and women with ageing is illustrated in Figure 7. These seemingly subtle differences in the way that our bones change with ageing contribute to our understanding of why fracture rates increase in women to a greater extent than in men.

Another aspect whereby men differ from women is in the mechanisms underlying age-related trabecular bone loss. In men trabecular thinning occurs and may be associated with decreases in IGF-1, whereas in women there is resorption and loss of trabeculae, particularly horizontal trabeculae, associated with oestrogen deficiency at the time of menopause104. This is another reason why skeletal fragility is higher in women.

**AGE 70 YEARS ONWARDS**

As men enter old age, the focus becomes prevention and treatment of osteoporosis with the objective of minimizing the risk of fragility fractures. Longitudinal studies suggest that the rate of bone loss accelerates after age 70 years in men109,110. As ageing progresses, bone loss in the marrow cavity is not compensated by bone deposition on the periosteum, which results in loss of cortical bone111. A systematic review established that men aged over 70 years were 50% more likely to suffer a fragility fracture than younger men112.

As indicated on the next page, secondary causes of osteoporosis are highly prevalent in men, the most common secondary causes being:
- Hypogonadism
- Glucocorticoid use
- Excessive alcohol use
- Smoking

Hypogonadism – as defined by a serum testosterone level less than 300 ng/dL – has been shown to be present in two-thirds of American male nursing home residents who have suffered hip fractures113 (see page 13).

**Prostate cancer and fractures**

Androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic prostate cancer and a significant risk factor for osteoporosis in older men114. Bone loss is rapid in men treated with ADT, of the order 2–4% at the lumbar spine and hip during the first year of treatment115,116. A U.S. study of more than 50,000 men who had received a diagnosis of prostate cancer in the 1990s evaluated fracture incidence117; 19.4% of men who took ADT had a fracture, as compared with 12.6% of those not receiving ADT, a highly statistically significant difference (P<0.001). All-cause mortality has also been shown to be higher for men taking ADT for prostate cancer, as compared to men with prostate cancer who were not taking ADT or men without prostate cancer118.

Daily alcohol intake of two or fewer units are not associated with increased fracture risk123. However, above this threshold, alcohol intake is associated with a 38% increased risk of suffering any fragility fracture and a 68% increased risk of hip fracture. Accordingly, with respect to bone health, moderation is best.

Smoking has negative effects on bone health124. Compared with non-smokers, current smoking is associated with a 29% increased risk of suffering a fragility fracture and an 84% increased risk of hip fracture. As it is for the heart and the brain, smoking is bad for your bones and should be avoided.

**FIGURE 7 The influence of bone geometry on bone strength**105

**LEFT**

For the same areal BMD, bone C has progressively greater bending strength and axial strength than bone B and bone A because the mass of bone C is distributed further away from the centre – adapted from Bouxsein106.

**RIGHT**

Sex and ageing differences in periosteal apposition and endocortical resorption in tubular bones. Adapted from Seeman107.
CAUSES OF OSTEOPOROSIS IN MEN

Secondary causes of osteoporosis in men, both common and rare, include:\n
Common
- Cushing’s syndrome or chronic corticosteroid use (>5 mg per day for more than 3 months)
- Excessive alcohol use (more than 2 units a day)
- Primary or secondary hypogonadism (serum testosterone levels <300 ng/dL)
- Inadequate calcium intake (<600 mg per day)
- Vitamin D deficiency/insufficiency
- Smoking
- Family history (genetics)

Less common
- Low body mass index (BMI <20)
- Lack of exercise or excessive exercise that leads to a low BMI
- 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 spondylitis
- Inflammatory bowel disease
- Malignancy, for example prostate cancer
  - Chemotherapy
  - Androgen deprivation therapy
- Warfarin

Rare
- Multiple myeloma
- Human immunodeficiency virus infection or its treatment with protease inhibitors (tenofovir)
- Mastocytosis
- Immunosuppressive therapy (cyclosporin, tacrolimus)
- Osteogenesis imperfecta
Hypogonadism – testosterone deficiency in men – occurs in up to 12.3% of men, and is a significant contributor to osteoporosis. The causes of male hypogonadism may be usefully categorized as primary or secondary:

**Primary hypogonadism** defects of the testes
- Genetic/chromosomal disorders (Klinefelter’s syndrome XXY)
- Anorchia (congenital or postorchidectomy)
- Cryptorchidism
- Chemotherapy (alkylating agents), radiotherapy
- Orchitis (mumps, HIV, autoimmune)
- Testicular trauma or torsion
- Medications (glucocorticoids, colchicine)
- Alcohol
- Chronic liver or kidney disease
- Haemochromatosis

**Secondary hypogonadism** defects of the hypothalamus or pituitary gland
- **Idiopathic**: Kallmann syndrome (anosmia and hypogonatrophic hypogonadism)
- **Functional**
  - Excessive exercise, weight change
  - Low BMI
  - Systemic or intercurrent illness
- **Structural**
  - Pituitary or hypothalamic tumour, prolactinoma
  - Infiltration (sarcoidosis, haemochromatosis, histiocytosis X, lymphoma)
  - Cranial irradiation, surgery, head trauma
- **Medications/Iatrogenic**
  - Androgen deprivation therapy for treatment of prostate cancer
  - Opioids, marijuana
  - Exogenous administration of androgens
Worldwide, a lack of awareness of the threat that osteoporosis poses to men is evident among men themselves, health-care professionals responsible for their care and the policymakers determining priorities within health systems. Three specific ‘gaps’ exist which will be considered in more detail: evidence-treatment gaps; gaps in clinical guidelines; and gaps in access to medicines.

**EVIDENCE-TREATMENT GAPS**

During the last decade, the observation that fracture begets fracture has underpinned major international\(^{125-127}\) and national initiatives\(^{128-139}\) intended to reduce the incidence of fragility fractures in men and women. The strategy shown in Figure 8, which was developed by the Department of Health in England in 2009\(^{140,141}\), serves to illustrate the systematic approach advocated by many of these leading initiatives.

Numerous audits conducted by IOF throughout the world have shown a pervasive and persistent osteoporosis care gap for patients who present with hip fractures or fragility fractures at other skeletal sites\(^{142-144}\). In the absence of a systematic approach the vast majority of fragility fracture sufferers do not receive the secondary preventive care that they need to prevent future fractures. Examples of this care gap for male fracture patients follow:

**Australia**: almost 38,000 patients (55% female, 45% male) aged 40 years or over were identified by 1,258 general practitioners in 2006–2007\(^{145}\). Among the 17,075 men, 6.8% had a prior fracture history. Overall, fewer than 30% of men and women with a prior fracture history received specific medication for osteoporosis. A recent analysis\(^{146}\) of the 45&Up study\(^{147}\) – a very large scale study of more than 213,000 older men and women in New South Wales – assessed rates of bone density testing and osteoporosis treatment. Two and a half times as many women had undergone bone density testing compared with men (22.5% versus 9.0%), and almost three and a half times as many women had received osteoporosis treatment compared with men (26.8% versus 8.0%).

**Canada**: osteoporosis treatment rates were evaluated for male participants in the Canadian Multicentre Osteoporosis Study (CaMos) who had suffered fragility fractures\(^{148}\). At the beginning of the study, just over 20% of men had a prevalent clinical fragility fracture, of which just 2.3% reported a diagnosis of osteoporosis and fewer than 1% were taking a bisphosphonate medicine. By year five of the study, 10.3% of the men who had a fracture at baseline, or had suffered a new fracture in the intervening 5 years, reported a diagnosis of osteoporosis. Furthermore, fewer than 10% of men who had
a fracture history at year five were receiving treatment for osteoporosis.

**Denmark**: national registers were used to identify patients born in 1945 or earlier who sustained a fracture between 1997–2004. Initiation of osteoporosis treatment in men with vertebral fractures increased from 8% in 1997 to 16.5% in 2004. For men with hip fractures, treatment rates increased from 0.7% in 1997 to 3.4% in 2004.

**Switzerland**: a nationwide survey of hospital Emergency Departments identified almost 5,000 consecutive patients who presented with one or more fractures between 2004–2006. Of the 870 men in the study, 13.8% were adequately treated for osteoporosis.

**The Netherlands**: the PHARMO database in the Netherlands was analysed to establish what proportion of patients hospitalized with a fragility fracture were treated with osteoporosis medicines during the year after fracture. Less than 5% of men with fractures were treated.

**United Kingdom**: in 2011, the Royal College of Physicians published findings from the national audit of falls and bone health in older people. Only 37% of local health services provided any kind of Fracture Liaison Service (FLS) and not all of these could demonstrate reliable assessment of all fracture patients. The proportion of men treated for osteoporosis after hip fracture was 47% for men aged less than 75 years and 55% for older men. The proportion of men treated for osteoporosis after a non-hip fragility fracture was 15% for men aged less than 75 years and 26% for older men.

**United States of America**: a nationally representative study of more than 51,000 patients admitted to one of 318 hospitals across the United States with a hip fracture between 2003–2005 assessed levels of secondary preventive care. Among men, 2.2% received osteoporosis medication. A recent study has shown an alarming reduction in the proportion of hip fracture patients being treated for osteoporosis in U.S. hospitals. For men and women combined, treatment rates have reduced from around 40% in 2002 to 20% in 2011. Men were 50% less likely to receive treatment than women. Another large-scale study of health insurance claims for fractures occurring in men between 2000 and 2005 found that 8% of men with a fragility fracture at any skeletal site received bisphosphonate treatment.

As highlighted previously in this report, both ADT and GC treatment are leading secondary causes of osteoporosis. Studies from several countries have evaluated osteoporosis assessment and treatment rates among men starting ADT:

**Canada**: among men treated with ADT at the Juravinski Cancer Centre in Hamilton, Ontario in 2008 and 2009, 28% were appropriately screened and managed for osteoporosis.

**United States of America**: a study of men treated with ADT in the Veterans Affairs health system in New Mexico evaluated osteoporosis care. Just 13% of men underwent BMD testing and 21% received treatment with an intravenous or oral bisphosphonate drug.

Similar low levels of osteoporosis assessment and treatment have been reported for men receiving glucocorticoid therapy. There are very few data on the use of glucocorticoids in men younger than
Assessment and treatment of men has not featured adequately in national clinical guidance in many countries.

50 years. The lack of prophylactic treatment for osteoporosis in men receiving GC is another cause of potentially avoidable fragility fractures.

United Kingdom: data from the General Practice Research Database (GPRD) have demonstrated that fracture risk is increased even with relatively low daily doses (2.5–7.5 mg) of prednisolone or its equivalent and rises further with increasing daily dose^{162}.

United States of a America: a study reported BMD measurement being performed in less than 5% of men, as compared with 13% of women, and osteoporosis treatment being initiated for fewer than 9% of men, as compared with 57% of women^{158}.

Canada: in the Canadian Osteoporosis Study (CaMos), the risk of incident fragility fractures over 10 years was significantly increased with prior use of glucocorticoids for a month or more^{163}.

GAPS IN CLINICAL GUIDELINES

Given that one-third of hip fractures occur in men, assessment and treatment of osteoporosis in men has not featured adequately in national clinical guidance in many countries. A good example of this oversight relates to guidance issued by the National Institute for Health and Clinical Excellence (NICE) in the UK.

Over the last decade, NICE has published a comprehensive suite of guidelines relating to prevention of fragility fractures among postmenopausal women. The first secondary fracture prevention treatment guideline was published in 2005^{164}. In 2008, a revised treatment guideline for secondary fracture prevention and a new primary fracture prevention guideline were published for women, and subsequently updated in 2011^{165,166}. In 2012, clinical management guidelines concerned with assessment of risk for fragility fracture did make mention of men^{167}. However, in the absence of specific treatment guidance for men, a key component of mandatory prescribing recommendations for the UK National Health Service is missing.

As men continue to live longer lives and suffer increasing numbers of fragility fractures – and hip fractures in particular – policymakers in all countries should ensure that new national clinical guidelines on osteoporosis management always include the care of men.

GAPS IN ACCESS TO MEDICINES

A consequence of the fact that the majority of the major phase III clinical trials conducted to fulfil drug registration requirements with the world’s regulatory authorities have been conducted in postmenopausal women is that osteoporosis medicines have been licensed to treat men, often, many years after they were first available for women. As considered in the next section of this report, the evidence-base for treatment of osteoporosis in men has grown substantially in the last decade and, as such, access to medicines to treat osteoporosis in men needs to keep pace with this progress.
This report has summarized the burden osteoporosis imposes upon men throughout the world, how osteoporosis develops in men and the current gaps in treatment, clinical guidelines and access to medicines. The take home message is that the vast majority of men who are at high risk of suffering fractures caused by osteoporosis are unaware of their risk, as are those delivering their health care. This status quo must be challenged, and this challenge is the focus of the last section of this report.

GUIDANCE FOR MEN

Who should be tested?

Men who have suffered a fracture as a result of a fall from standing height or less since age 50 years should undergo assessment for osteoporosis and fracture risk. In addition to those who have fractured, based on the recommendations of the Endocrine Society in the United States, men with the following common risk factors for osteoporosis should have BMD measured:

- **Causes related to modifiable lifestyle factors:**
  - Excessive alcohol consumption
  - Smoking
  - Excessive exercise

- **Causes related to nutritional deficiencies:**
  - Eating disorders and low BMI
  - Malabsorption
  - Vitamin D deficiency

- **Causes related to diseases and their treatments:**
  - Chronic kidney disease
  - Chronic obstructive pulmonary disease
  - Delayed puberty
  - Glucocorticoid excess (endogenous or exogenous)
  - HIV and protease inhibitor therapy
  - Hypercalciuria
  - Hypogonadism (including Androgen Deprivation Therapy)
  - Inflammatory arthritis
  - Mastocytosis
  - Multiple myeloma
  - Osteogenesis imperfecta
  - Primary hyperparathyroidism
  - Thyrotoxicosis

Men with these risk factors should ask their doctor the following questions:

- I have a common risk factor for osteoporosis, so do you agree that I should have a bone density test done? How often should it be repeated?
- Can you calculate my risk of suffering future fractures?
- What should I be doing with respect to calcium, vitamin D and exercise?
- Can you advise me of specific lifestyle changes I can make to improve my bone health?
- Do I need specific therapy to treat osteoporosis?

**Lifestyle measures**

Exercise has been shown to improve BMD in older men\(^{171}\) and decrease falls risk\(^{172}\). Accordingly, the U.S. Endocrine Society recommends that men at risk of developing osteoporosis should participate in weight-bearing activities – such as walking – for 30–40 minutes per session, 3–4 sessions per week\(^{170}\).

Men should maintain adequate dietary intake of calcium in accordance with the recommended national daily intake in their country. The Endocrine Society has specified 1,000–1,200 mg as an appropriate level for the United States, with the option of calcium supplementation if dietary intake does not achieve this level\(^{170}\). Vitamin D, the primary source of which is via sun exposure, plays a major role in bone health. Recommendations from Osteoporosis Australia highlight the need for regular and safe sunlight exposure, which aims to avoid skin redness and any attendant increased risk of developing skin cancer\(^{66}\). Clearly, safe levels of sunlight exposure depend on latitude and season of the year, so men should consider appropriate guidance for their own country of residence. The Australian\(^{66}\), U.S.\(^{170}\) and IOF\(^{173}\) recommendations identify a serum 25-hydroxyvitamin D level of 75 nmol/L (30 ng/ml) as optimal for reducing risk of fractures.

**GUIDANCE FOR HEALTH-CARE PROFESSIONALS**

The assessment and treatment of osteoporosis in men has been the subject of several recent review articles\(^{111,174,175}\). A summary of the benefits of the various osteoporosis treatments provided in one review is illustrated in Table 1. A précis of the evidence-base for the individual treatments follows.

**Bisphosphonates**

**Alendronate**: many studies have evaluated the efficacy of alendronate in men with osteoporosis. The most recent confirmed findings of previous studies with regards to improved BMD and reduced bone turnover markers\(^{176}\). Fracture reduction was demonstrated in a study of men with hypogonadism or eugonadism (normal testosterone levels)\(^{177}\). The incidence of radiologically detected vertebral fractures was 0.8% in the patients taking alendronate as compared to 7.1% in the controls. A cost-effectiveness analysis supports the use of alendronate in men with primary osteoporosis who are at high fracture risk\(^{178}\). Alendronate has also been shown to improve BMD for patients receiving ADT\(^{178}\) or GC\(^{179}\).

**Risedronate**: Risedronate has been shown to increase BMD\(^{180}\) and, in the context of a non-blinded study, reduce vertebral fracture incidence in primary osteoporosis in men\(^{181}\).

**Intravenous bisphosphonates**: monthly intravenous (i.v.) ibandronate therapy has been shown to improve BMD and bone turnover markers in men with osteoporosis\(^{182}\). In men receiving ADT, i.v. pamidronate has been shown to prevent bone loss\(^{183}\). The most well studied i.v. bisphosphonate in men is zoledronic acid, which has been shown to improve BMD\(^{176,184}\) and reduce the incidence of both vertebral\(^{184}\) and nonvertebral fractures\(^{185}\) in men with primary osteoporosis. Zoledronic acid has also improved BMD for men receiving ADT\(^{186}\) and GC\(^{187}\).

**Alternative and adjunctive therapies**

**Denosumab**: a fully human monoclonal antibody which is an alternative to bisphosphonate therapy. Denosumab has been shown to improve BMD in men with primary osteoporosis\(^{188}\), and improve BMD and reduce vertebral fracture incidence in men taking ADT\(^{189}\). In a study of Japanese men and women with

### TABLE 1 Summary of benefits of osteoporosis therapy in men\(^{111}\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary osteoporosis</th>
<th>Androgen deprivation therapy</th>
<th>Osteoporosis secondary to glucocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMD</td>
<td>Vertebrae fracture</td>
<td>Non-vertebrae fracture</td>
</tr>
<tr>
<td>Alendronate</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Risedronate</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Denosumab</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

Exercise has been shown to improve BMD in older men and decrease falls risk.

osteoporosis, denosumab significantly reduced the incidence of new or worsening vertebral fracture by almost 66% in two years\textsuperscript{190}.

**Teriparatide:** the primary anabolic agent for the treatment of osteoporosis, teriparatide has been shown to increase BMD\textsuperscript{191} in men with hypogonadism or eugonadism and osteoporosis, and reduce vertebral fracture incidence\textsuperscript{192}. Teriparatide has also been shown to prevent bone loss\textsuperscript{193,194} in men and vertebral fractures in men and women with GC-induced osteoporosis\textsuperscript{195}. Teriparatide treatment also showed larger improvements in spinal BMD, microstructure, and finite element-derived bone strength than risedronate in men with GC-induced osteoporosis\textsuperscript{196}.

**Testosterone:** studies of testosterone as a treatment for osteoporosis are limited and no study has used fracture as a primary endpoint. Testosterone therapy has been shown to improve BMD and bone turnover markers in men with hypogonadism\textsuperscript{196,197}. Whilst studies combining testosterone and bisphosphonates have not been conducted, a rationale exists for bisphosphonate use in men receiving sex steroids to restore eugonadism\textsuperscript{175}.

**Clinical guidelines for osteoporosis treatment in men**

The following clinical guidelines provide clinicians with more detailed analysis and recommendations regarding osteoporosis treatment in men:

**Australia:** Clinical Guideline for the Prevention and Treatment of Osteoporosis in Postmenopausal Women and Older Men. 2010. The Royal Australian College of General Practitioners\textsuperscript{188}.

**Germany:** 2006 DVO-guideline for prevention, diagnosis, and therapy of osteoporosis for women after menopause, for men after age 60 - executive summary guidelines\textsuperscript{199}.

**Japan:** Japanese 2011 guidelines for prevention and treatment of osteoporosis - executive summary\textsuperscript{200}.

**United Kingdom:** Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013\textsuperscript{201}.

**United States of America:** Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline\textsuperscript{170}.

IOF Scientific Working Groups have published position papers relating to the prevention and treatment of osteoporosis in men receiving ADT and GCs:

- Cancer-associated bone disease\textsuperscript{202}.
- A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis\textsuperscript{203}.

**GUIDANCE FOR POLICYMAKERS**

Given that one-third of hip fractures occur in men\textsuperscript{6} and the number of older men throughout the world is increasing very rapidly\textsuperscript{1,2} combined with the fact that mortality after hip fracture is higher in men. Policymakers have a critical role to play in enabling health-care professionals to reduce the incidence of fragility fractures in men. This will also significantly reduce the financial burden that fractures caused by osteoporosis place on national health-care systems, now and in the future. The following issues should be prioritized by policymakers:

**Fracture Liaison Services:**

individuals who have suffered a first fragility fracture are at considerably increased risk of suffering second and subsequent fractures\textsuperscript{204,205}. In the absence of a systematic approach to delivery of secondary fracture prevention, the vast majority of fragility fracture patients do not receive the osteoporosis care that they need\textsuperscript{142,143}.

Fracture Liaison Services (FLS) have been demonstrated to provide clinically effective care in a highly cost-effective manner in a growing number of countries throughout the world\textsuperscript{206,207}. Governments in several countries have explicitly endorsed their implementation as a means to close the current global care gap\textsuperscript{132,133,140,141,208-210}. The IOF Capture the Fracture Campaign\textsuperscript{125,126,168} serves as a global hub for resources developed to support policymakers and health-care professionals in the implementation of FLS. IOF has also developed globally endorsed standards for FLS\textsuperscript{168}:

**www.capturethefracture.org**

**National clinical guidelines:**

national guidelines development groups and/or national health-care quality agencies have published guidelines on the treatment and clinical care of osteoporosis in women. However, a comparative vacuum exists regarding national guidance on the treatment of osteoporosis in men. Policymakers should ensure that national guidelines on osteoporosis developed by government agencies always address osteoporosis in both men and women.

**Access to medicines:** access to medicines for osteoporosis is highly variable throughout the world. Policymakers should ensure that access to osteoporosis treatments, and reimbursement mechanisms, do not discriminate against men.

**Support national education and awareness campaigns:** helping to raise public awareness of the preventive actions that can be taken to reduce risk of bone muscle and joint diseases will avoid escalating costs to health-care systems and the pain, death and suffering of millions of people.
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OSTEOPOROSIS IN MEN – WHY CHANGE NEEDS TO HAPPEN

It’s not just a woman’s disease
The common misconception is that osteoporosis affects only women, but it affects millions of men around the world too, with devastating consequences. The facts:

- Osteoporosis affects men too
- Fractures rates are increasing rapidly in men
- Men more likely than women to be disabled or die from osteoporosis
- Fractures in men are costly to health-care systems
- Fractures cause loss of work days
- Poor lifestyle in boys and men impact their future risk of osteoporosis

- Men are not being diagnosed and treated for osteoporosis
- Men can take steps to build strong bones and prevent fractures

Make change happen
Osteoporosis and related fractures pose a serious and growing threat to the health and well-being of men around the world. IOF joins national patient and medical societies worldwide in calling for concerted efforts on the part of governments and health professionals to reduce the burden of osteoporosis in the male population. Measures must be taken to:

- Encourage and support efforts to increase awareness of osteoporosis risk among men
- Improve knowledge within the health professional community so that at-risk men are identified and treated
- Support the development and dissemination of osteoporosis management guidelines targeted to men
- Promote research into osteoporosis in men
- Facilitate reimbursement of osteoporosis testing and treatment in men at risk
- Implement systems of care to prevent secondary fragility fractures so that men who have suffered a fracture are identified and treated in a timely manner
REFERENCES


121. Accessed 21 June 2013


Osteoporosis poses a serious and growing threat to the health and well-being of millions of men worldwide. Unfortunately, the disease is often under-diagnosed and under-treated which is leading to early death and disability. Often mistakenly considered a woman’s disease, osteoporotic fractures affect one in five men globally. In fact, one-third of all hip fractures worldwide occur in men and they are twice as likely as women to die from them. This report highlights the cost-effective evidence-based solutions that governments, health authorities and medical professionals must implement to help prevent and control osteoporosis in men.

PROF CYRUS COOPER
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