Medical Background

Osteoporosis in Men

Osteoporosis Learning Program

MERCK
Human Health

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Osteoporosis in Men

Learning Objectives

After reading this clinical overview, you should be able to:

- Describe the epidemiologic patterns of the following osteoporotic fractures in men:
  - hip fractures
  - vertebral fractures
  - other fractures (including the radius/ulna, humerus, pelvis, and femoral shaft).
- List risk factors which may predispose men to osteoporotic fractures.
- Discuss why men are less predisposed to have fragile bones than women.
- Describe the effects of the following factors on bone mass in men:
  - advancing age
  - sex steroid levels (androgens).
- Describe primary and secondary causes of osteoporosis in men:
  - age-related changes
  - idiopathic (no known cause)
  - long-term use of certain drugs (eg, chronic glucocorticoid therapy)
  - certain medical conditions (eg, hypogonadism).
- Explain the relationship between bone mass and fracture risk in men.
- Discuss the role of bone mass measurements in men.
- Summarize selected findings of the pivotal clinical trial which evaluated the efficacy and tolerability of alendronate for the treatment of osteoporosis in men.

Introduction

Osteoporosis in men is a therapeutic area in which new knowledge and further understandings are constantly evolving. The purpose of this educational piece is to provide background information regarding osteoporosis in men. This document highlights key points on the epidemiology, pathophysiology, evaluation, and management of osteoporosis in men based on published literature. An overview of the key clinical trial that evaluated the use of FOSAMAX® (alendronate sodium) for the treatment of osteoporosis in men is also presented.

Epidemiology of Osteoporotic Fractures in Men

Epidemiologic reports have shown that age-related increases in osteoporotic fractures are evident in men as well as in women, and represent an important public health issue. The incidence of all fractures is higher in men than women from adolescence through middle life, probably due to trauma. The reversal of this trend after this age appears to be due to the increased incidence of fractures of the pelvis, humerus, forearm, and femur in women beginning at age 40 to 50. The incidence of fractures due to minimal or moderate trauma (particularly in the hip and spine) increases rapidly in aging men.

Hip Fractures

- An exponential rise in the incidence of hip fractures occurs in both men and women as they age. However, the increase in fracture incidence occurs 5 to 10 years later in men.
- In the U.S., the incidence of hip fractures is higher in women than men. A 2:1 ratio of women-to-men has been reported for the incidence of hip fractures. For example, the incidence of hip fractures in 1000 women over age 65 in the U.S. is 8 to 10 compared with an incidence of 4 to 5 per 1000 similarly aged men.
- Differences in the incidence of hip fractures among men exist depending on race and geographic location:
  - African-American men experience half the rate of hip fractures as Caucasian men
  - Japanese men living in Japan or Hawaii have a lower rate of hip fractures than Caucasian men in the U.S.
  - Men in southern Europe and Asia have as many hip fractures as women, although the overall incidence in both genders is lower compared with the U.S., northern Europe, and Australia.
- At present, men experience about 25% to 30% of all hip fractures worldwide. The number of hip fractures in men is projected to increase dramatically as the male population ages. By the year 2025, the number of hip fractures occurring annually in men is expected to exceed 1.1 million worldwide. This figure is close to the incidence of 1.2 million hip fractures among women worldwide in 1990.
- Mortality after hip fractures has been shown to be higher in men age 75 and older than women of the same age. A recent study reported that the mortality rate during the first 1 to 2 years after a hip fracture was higher in men than women (42.4% vs. 23.3%, p=0.001). In this study, the observed gender difference in the mortality rate after hip fracture was not explained by medical comorbidity, age, functional limitation, and other factors significantly associated with survival. The cause of this increased vulnerability to mortality warrants further investigation and emphasizes the need and urgency to identify men with low bone mass or osteoporosis before their first fracture.

Vertebral Fractures

- According to some U.S. data, the **incidence** of vertebral fractures in men is about half of that in women. Some studies have shown that the **prevalence** of vertebral fractures is actually higher in men up to the age of 60 than women (believed to be due to the increased occurrence of early life trauma).
- Men with vertebral fractures have lower bone density compared with controls suggesting that low bone mass contributes to vertebral fracture risk as in women.
- In men, vertebral fractures occur predominantly in the low thoracic vertebrae although they can be found at all levels of the spine.
- Most vertebral fractures in men are anterior compression in type, with vertebral crush fractures occurring less frequently in men than women. Vertebral fracture in men is associated with loss of height, kyphosis, increased risk of other fractures, and increased disability as seen in women.

Other Fractures

- Other fractures (including fractures of the radius/ulna, humerus, pelvis, and femoral shaft) share similar epidemiologic patterns in men and women, although men generally experience more of these types of fractures during their youth due to trauma.
- In men, the incidence of limb fractures (mainly lower limb fractures) related to trauma remains relatively stable during midlife and begins to increase ***after age 75*** due to osteoporosis.
- In men, the occurrence of a distal forearm fracture or a tibial fracture indicates an increased risk for subsequent hip fracture. (Such an incident fracture presumably identifies an individual as being at risk for future fractures and may signify the presence of other factors such as low bone mass, increased risk of falling, or both.)

incidence
rate at which a new event occurs over time.

prevalence
number of cases of a disease present in a population at a specified time.

Pathophysiology and Clinical Determinants of Osteoporosis in Men

The underlying pathophysiology of osteoporosis for both men and women is the net negative balance in bone remodeling that occurs when the rate of bone resorption exceeds the rate of bone formation. Several studies have suggested that an important factor of bone loss in men is reduced bone formation in addition to increased bone resorption, which predominates in the pathogenesis of osteoporosis in postmenopausal women.

Risk Factors

The following have been identified as key risk factors for osteoporotic fractures in men. They are similar to those reported in women.

- Low bone mineral density (BMD)
- Low body mass
- Advancing age
- Smoking
- Excessive alcohol intake
- Physical inactivity
- Increased tendency for falls (for hip fractures)

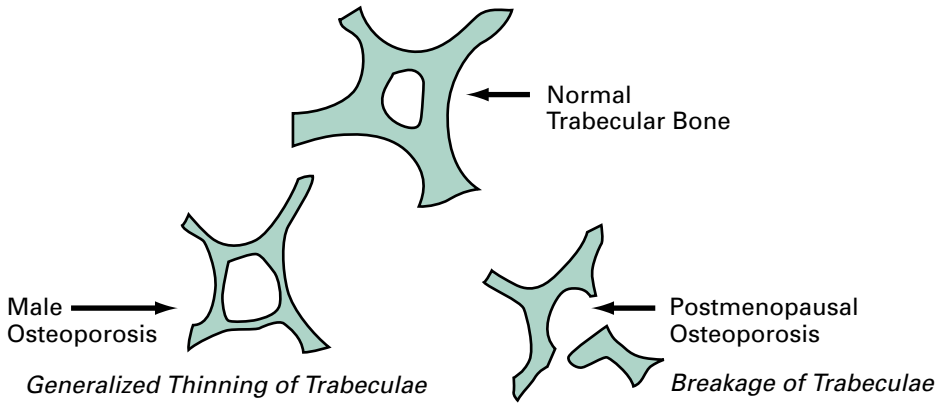
Bone Mass

- Men are less predisposed to have fragile bones than women because men generally have:
  - greater peak bone mass and larger cross-sectional bone surface
  - less trabecular bone loss
  - trabecular bone loss occurring by a pattern of trabecular thinning rather than by **trabecular perforation** (Figure 1 shows the difference between trabecular thinning and perforation.)
  - less cortical bone thinning due to less resorption at the inner surfaces of the cortical bone and greater expansion in the **periosteum** which maintains the mechanical strength and geometry of bone.
- Low peak bone density may play a role in the development of osteoporosis in men.

trabecular perforation resorption causing trabecular thinning that results in a loss of connection between trabecular plates.

periosteum specialized connective tissue that covers all bones in the body.

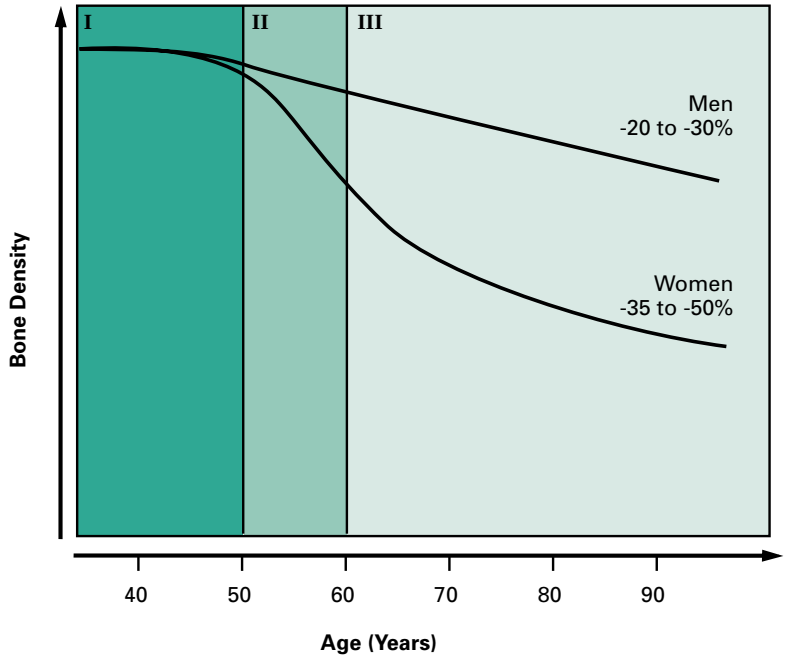
Figure 1. Patterns of Trabecular Bone Loss



Age-related Changes in Bone Mass

- Aging in men is associated with trabecular and cortical bone loss. Over their lifetimes, men may lose about 20% to 30% of their total bone mass, whereas women may lose approximately 35% to 50% of their total bone mass. (See Figure 2 on page 8.)
- After menopause, the annual rate of bone loss in women is generally around 1% to 2%, but may be as high as 3% to 5% during the first 5 to 8 years after menopause. The literature quotes a lower rate of bone loss in men, an average of 0.2% to 0.5% per year.
- The age-related decline in trabecular bone density appears to occur at a similar rate in men and women, but differs in the pattern of trabecular bone loss. Men tend to lose bone by trabecular thinning (resulting in a decrease in trabecular width) whereas women experience high bone turnover (associated with estrogen deficiency during menopause) leading to bone loss by trabecular perforation (resulting in a decrease in trabecular number).
- In longitudinal studies, the rate of age-related loss in cortical bone density in men is reported to be rapid at 5% to 10% per decade. Previous estimates of rate of bone loss in cross-sectional studies are reported as 1% to 3% per decade.

Figure 2. Bone Loss During Adult Life



I **Premenopause –** slight bone loss

II **Postmenopause –** accelerated bone loss

III **More than 10 years Postmenopause –** bone loss continues but at lower rate

androgen
a substance, such as testosterone, that promotes masculinization.

hypogonadism
a condition resulting from abnormally decreased function of the gonads leading to retardation of growth, and interference with sexual development and maintenance of secondary sex characteristics depending on the age of occurrence.

Sex Steroid Levels

- Sex steroids (both **androgens** and estrogens) appear to influence the regulation of bone metabolism through complex cellular mechanisms involving osteoblasts and osteoclasts. Androgen receptors are present in osteoblasts and, thus, can affect a variety of osteoblastic functions including proliferation, growth factor and cytokine production, and bone matrix protein production. Androgens may dampen bone resorption through inhibition of osteoclast action via modulation of bone regulatory hormones such as parathyroid hormone (PTH) and insulin-like growth factor-1 (IGF-1).
- The correlation between the decline in androgen concentrations during aging and effects on decreasing bone mass and increasing fracture risk in men is inconclusive at this point. Some studies have suggested a weak correlation between androgen levels and measures of bone density, whereas others have not documented effects of androgens on bone.
- **Hypogonadism** is an accepted cause of secondary osteoporosis in men. The importance of androgen action in the *achievement of peak bone mass* is supported by evidence of reduced bone mass found in hypogonadism occurring in males before puberty. Androgens also appear to be essential for the *maintenance of bone mass* in adult men as suggested by the low bone mass associated with hypogonadism which occurs after puberty.

- Selected case reports of severe osteopenia in men with estrogen deficiency (estrogen receptor abnormality or absent **aromatase** enzyme activity) have raised questions about the role of estrogens in maintaining bone mass in men.

aromatase
an enzyme which catalyzes the conversion of testosterone to estradiol.

Other Causes of Low Bone Mass

- Certain systemic diseases (eg, hypogonadism, hyperthyroidism) and drugs (eg, glucocorticoids, certain anticonvulsants) may increase bone loss and contribute to secondary osteoporosis.
- Marked weight loss appears to be associated with greater rates of bone loss.

Relationship Between Bone Mass and Fracture Risk

- As bone mass in women decreases, fracture risk increases. This has been demonstrated in both retrospective case-controlled studies and prospective trials in women. Although fewer data are available in men, they are consistent with a similar inverse relationship of decreasing bone mass to increasing fracture risk.
- The World Health Organization (WHO) did not develop specific categories for osteoporosis in men when they identified the categories for postmenopausal women in 1994 (data on men are less extensive).
- For postmenopausal women, the WHO categories defined osteopenia as a T-score of -1.0 to -2.5 standard deviations (SD) and osteoporosis as a T-score <-2.5 SD. T-score was developed to relate BMD to fracture risk. A woman's BMD is calculated by comparing it to normal women at their peak bone mass (female normative database). When the WHO definitions were applied to the U.S. male population specifically using reference ranges for young adult men at their peak bone mass (male normative database), it was learned that 47% of men age 50 and older have osteopenia at the femoral neck and 6% have osteoporosis. But whether a cut point of a T-score of more than 2.5 SD below young adult peak mean in men is appropriate for identifying men with osteoporosis is yet to be determined.
- A recent analysis suggests that the same T-score threshold for osteoporosis in postmenopausal women may be applicable to men because of the similarity of the median bone mass T-scores in patients who experienced fractures, but these results need to be confirmed in a prospective study.
- More clinical experience is needed to determine if using the WHO categories of osteoporosis as defined for women are equally appropriate and satisfactory to predict fracture risk in men.

Falls

- There are few prospective data that *directly* relate fall propensity to subsequent fractures in men.
- Several factors *indirectly* related to the risk of falling (eg, nutritional deficiencies, frailty, certain medical conditions such as neurologic or visual impairment, history of stroke or dementia) have been associated with fracture in both men and women.
- Some studies suggest that falls are less common in older men than women, and that women fall more often on their hips and forearms than men.

Evaluation of Osteoporosis in Men

Osteoporosis in men encompasses several potential etiologies. A general approach to the evaluation of osteoporosis in men can be formulated with the constraints that these guidelines are based on limited existing knowledge of disease epidemiology and clinical characteristics. Certain clinical situations should raise suspicion of the presence of osteoporosis in men, such as a history of low-trauma fractures in the absence of evidence of another pathologic process. Vertebral compression fractures on routine chest X-rays or radiographic signs of reduced bone mass, even in the absence of a fracture, should prompt a fuller osteoporosis evaluation and BMD assessment. The presence of one or more secondary causes of osteoporosis should prompt the consideration of a metabolic bone evaluation.

Primary Osteoporosis

The classification of primary osteoporosis includes age-related and idiopathic forms of osteoporosis.

- Age-related osteoporosis in men is defined as osteoporosis that occurs after age 70.
- The age of men with idiopathic osteoporosis varies widely over age 23 to 86 (with an average age in the mid-60s) and can overlap with age-related osteoporosis.
- One-third of all osteoporotic men are said to have a diagnosis of idiopathic osteoporosis.
- The characterization of idiopathic osteoporosis in men is not distinct, and studies have failed to show consistent biochemical or histomorphometric features. The initial presentations of men with idiopathic osteoporosis are usually symptoms of acute fracture or back pain.

Secondary Osteoporosis

To date, recognized osteoporosis in men has been predominantly diagnosed in association with secondary causes. Some studies have noted that the number of men with osteoporosis secondary to other disorders is higher than women, whereas other evaluations suggest that the proportion of men and women with secondary osteoporosis is actually very similar. There may be a detection bias explaining the discrepancy in these observations.

- Secondary osteoporosis may occur with the long-term use of certain drugs, including glucocorticoids, excessive doses of thyroxine, heparin, and certain anticonvulsants.
- Secondary osteoporosis may also be associated with numerous medical conditions including various endocrine disorders (eg, hypogonadism, hyperthyroidism, hyperadrenocorticism, diabetes mellitus, and others) and malabsorption syndromes (eg, those caused by gastrointestinal surgery).

- Some statistics in the literature state that hypogonadism and primary osteoporosis (which includes age-related and idiopathic forms) together account for about 60% of all cases of osteoporosis in men, while glucocorticoid-induced osteoporosis accounts for about 20% of all cases of osteoporosis in men.

Initial Evaluation of Osteoporosis: Medical History, Physical Examination, and Biochemical Measures

- Goals of an osteoporosis evaluation should be to identify the factors contributing to low bone mass in men.
- Complete medical history and physical examination are central to the evaluation of a man with low bone mass.
- The following laboratory tests may be considered in the initial evaluation to determine the cause of low bone mass: creatinine, calcium, phosphorus, alkaline phosphatase, testosterone, 25-hydroxyvitamin D, liver function tests, and complete blood count. Additionally, testing 24-hour urine calcium and creatinine may help identify idiopathic hypercalciuria, testing 24-hour urine cortisol may help identify hyperadrenocorticism, and testing thyroxine (T_4) and serum thyroid-stimulating hormone levels may help identify hyperthyroidism as potential causes of secondary osteoporosis.

Bone Mass Measurements

- Similar to women, BMD determinations are used in men to confirm the diagnosis of low bone mass, gauge its severity, and serve as a baseline from which to judge the progression or improvement of disease.
- BMD testing should be considered in men who present with findings suggestive of osteoporosis, such as low-trauma fractures, vertebral fractures on routine chest X-rays, radiographic criteria indicating a reduction in bone mass, or concomitant conditions or drugs associated with bone loss (eg, hypogonadism or chronic glucocorticoid use, respectively).
- Some leading clinicians recommend that men over age 75 (the approximate age at which fracture rates increase rapidly) are appropriate candidates for BMD screening.

Key Points

- Epidemiologic reports have shown that age-related increases in osteoporotic fractures are evident in men (not only in women), and represent an important public health issue.
- An exponential rise in the incidence of hip fractures occurs in both men and women as they age. Although hip fractures occur at a higher incidence in women compared with men (2:1 ratio) in the U.S., men experience about 25% to 30% of all hip fractures worldwide.
- Men demonstrated a greater risk of death 2 years after a hip fracture than women. The cause of this increased vulnerability to mortality warrants further investigation and emphasizes the need and urgency to identify men with low bone mass or osteoporosis before their first fracture.
- According to some U.S. data, the *incidence* of vertebral fractures in men is about half the incidence in women. Some studies have shown that the *prevalence* of vertebral fractures is actually higher in men up to the age of 60 than women (probably due to early life trauma).
- Vertebral fracture in men is associated with loss of height, kyphosis, increased risk of other fractures, and increased disability as seen in women.
- Other fractures (including fractures of the radius/ulna, humerus, pelvis, and femoral shaft) share similar epidemiologic patterns in men and women, although men generally experience more of these types of fractures during their youth due to trauma.
- In men, the incidence of limb fractures (mainly lower limb fractures) related to trauma remains relatively stable during midlife and begins to increase in men after age 75 due to osteoporosis.
- Key risk factors which may predispose men to osteoporotic fractures are: low BMD, low body mass, advancing age, smoking, excessive alcohol intake, physical inactivity, and increased tendency for falls (for hip fractures).
- Men are less predisposed to have fragile bones than women because men have: greater peak bone mass and larger cross-sectional bone surface, less trabecular bone loss, trabecular bone loss occurring by trabecular thinning rather than by trabecular perforation, and less cortical bone thinning.
- Aging in men is associated with trabecular and cortical bone loss.
- Sex steroids (both androgens and estrogens) appear to influence the regulation of bone metabolism through complex cellular mechanisms involving osteoblasts and osteoclasts. Some studies have suggested a weak correlation between androgen levels and measures of bone density, whereas others have not documented effects of androgens on bone.

- The importance of androgen action in the *achievement of peak bone mass* is supported by the evidence of reduced bone mass found in hypogonadism occurring in males before puberty. Androgens also appear to be essential for the *maintenance of bone mass* in adult men as suggested by the low bone mass associated with hypogonadism which occurs after puberty.
- Primary osteoporosis includes age-related and idiopathic forms of osteoporosis. Age-related osteoporosis in men is defined as osteoporosis which occurs after age 70. The age of men with idiopathic osteoporosis varies widely over age 23 to 86 (with an average age in the mid-60s) and can overlap with age-related osteoporosis. Idiopathic osteoporosis represents one-third of all men with the disease. The initial presentations of men with idiopathic osteoporosis are usually symptoms of acute fracture or back pain.
- Some statistics in the literature state that primary osteoporosis (which includes idiopathic and age-related forms) and hypogonadism together account for about 60% of all cases of osteoporosis in men, whereas glucocorticoid-induced osteoporosis accounts for about 20% of all cases of osteoporosis in men.
- Secondary osteoporosis in men may occur with the long-term use of certain drugs (eg, glucocorticoids) and may also be associated with certain medical conditions (eg, hypogonadism).
- Although fewer data are available in men, they are consistent with an inverse relationship of decreasing bone mass to increasing fracture risk.
- Similar to women, BMD determinations can be used in men to confirm the diagnosis of low bone mass, gauge its severity, and serve as a baseline from which to judge the progression or improvement of disease.
- BMD measurements should be considered in men who present with any of the following findings:
  - low-trauma fractures
  - vertebral fractures on routine chest X-rays
  - radiographic signs of reduced bone mass
  - concomitant drugs or conditions associated with bone loss (eg, chronic glucocorticoid use or hypogonadism, respectively)
  - advanced age (>75 years, the approximate age at which fracture rates increase rapidly).

Treatment of Osteoporosis in Men

When recognized as a problem for men, the management of osteoporosis had been based on treatment regimens used in postmenopausal women with osteoporosis. Along with bisphosphonates (eg, alendronate, etidronate, and pamidronate) and calcitonin, an array of other agents have been used in the treatment of osteoporosis in men including calcium and vitamin D, thiazide diuretics, fluoride, parathyroid hormone, and growth hormone. Many of these agents have only been studied in small or uncontrolled trials. Androgen replacement has also been used since testosterone has been shown to be effective in modestly increasing BMD in hypogonadal men. Testosterone replacement has also been used in **eugonadal** men with osteoporosis, although its value is less well established.

eugonadal
associated with normal levels of pituitary gonadal hormones.

FOSAMAX (alendronate sodium) for the Treatment of Osteoporosis in Men: Study Summary

To date, alendronate is the first agent studied in the largest, randomized, placebo-controlled trial conducted in the male osteoporotic population. The efficacy and tolerability of oral alendronate was evaluated in a multinational, double-blind, placebo-controlled, 2-year study of men with osteoporosis (femoral neck T-score ≤-2.0 and lumbar spine T-score ≤-1.0 *or* femoral neck T-score ≤-1.0 and a history of an osteoporotic fracture). The mean femoral neck T-score was -2.2. At baseline, about 50% of men had prevalent vertebral fractures and 36% were androgen deficient (low serum free testosterone). Men with secondary causes of osteoporosis, other than low serum free testosterone levels, were excluded from the study. A total of 241 men between age 31 to 87 (mean age, 63) were randomized to receive either alendronate 10 mg once daily (n=146) or placebo (n=95). All men took calcium (500 mg/day) and vitamin D (400–450 IU/day) supplements. The main efficacy measures were the percent changes from baseline in BMD of the lumbar spine (primary endpoint), hip, and total body which were measured by dual-energy X-ray absorptiometry at baseline and 6, 12, 18, and 24 months of the study. The analysis of the efficacy data was based on the intention-to-treat principle. Incident vertebral fractures were assessed semiquantitatively by comparison to baseline X-rays and by quantitative digitization of X-rays at a central site by blinded personnel. Measurements of biochemical markers of bone turnover were also obtained. Safety and tolerability were assessed by review of clinical and laboratory safety parameters. Table 1 summarizes the design of the study.

Table 1. Alendronate for the Treatment of Osteoporosis in Men: Summary of Study Design

Design	Randomized, double-blind, placebo-controlled trial
Duration	2 years
Participants	241 men with osteoporosis (femoral neck T-score ≤ -2.0 and lumbar spine T-score ≤ -1.0 *or* femoral neck T-score ≤ -1.0 and a history of osteoporotic fracture)
Age	Range: 31-87 years Mean: 63 years
Baseline Characteristics	36% were androgen deficient (low serum free testosterone) 50% had prevalent vertebral fractures Mean femoral neck T-score = -2.2
Treatment Groups	Alendronate 10 mg once daily (n=146) Placebo (n=95) All patients received calcium (500 mg/day) and vitamin D (400–450 IU/day) supplements.
Endpoints	Primary: • Change in lumbar spine BMD Additional: • Change in BMD of femoral neck, trochanter, hip, and total body • Relationship between changes in BMD and baseline characteristics • Effect on biochemical markers of bone turnover • Safety/tolerability

The results showed that alendronate increased lumbar spine BMD regardless of age, femoral neck T-score, prevalent vertebral fractures, or gonadal status (testosterone levels). Alendronate significantly increased lumbar spine BMD by 7.1% from baseline over the 2 years of the study. These increases were significant by month 6 and continued throughout the duration of the study. The effects of alendronate on lumbar spine BMD were similar in androgen-deficient men and those with normal serum free testosterone levels at baseline. Alendronate also significantly increased femoral neck BMD by 2.5% and total body BMD by 2.0% compared with placebo ($p<0.001$ for all comparisons). Statistically significant changes in BMD were also seen at the trochanter and hip.

Alendronate also reduced the incidence of vertebral fracture and prevented decreases in height. The incidence of vertebral fractures was significantly lower ($p=0.02$) in men taking alendronate (0.8% [n= 1]) compared with placebo (7.1% [n= 7]), as noted by quantitative methods. Men taking alendronate had a 0.6 mm decrease in height compared with a decrease of 2.4 mm in those taking placebo ($p=0.02$ for the difference between groups). Table 2 summarizes the results of alendronate on increasing spine, hip, and total body BMD, reducing vertebral fracture incidence, and preventing changes of height.

Table 2. Alendronate for the Treatment of Osteoporosis in Men: Changes in BMD, Fracture Incidence, and Height

Endpoints	Alendronate	Placebo	p-value Alendronate vs. Placebo
Changes in BMD			
Lumbar spine	+7.1%	+1.8%	<0.001
Femoral neck	+2.5%	-0.1%	<0.001
Trochanter	+4.3%	+1.3%	<0.001
Hip	+3.1%	+0.6%	<0.001
Total body	+2.0%	+0.4%	<0.001
Fracture Incidence			
Vertebral (quantitative)*	0.8%	7.1%	0.02
Vertebral (semiquantitative)**	3.1%	8.1%	0.12
Non-vertebral	4.1%	5.3%	0.8
Changes in Height	-0.6 mm	-2.4 mm	0.02

*Determined by quantitative evaluation of digitized X-rays at a central site.
**Determined by visual comparison to baseline X-rays without direct measurement.

After 2 years of treatment, there was a significant difference ($p<0.001$) in the bone resorption marker NTx (urine N-telopeptide of type I collagen corrected for creatinine) resulting in a 59% mean decrease in NTx in men taking alendronate compared with a 9% reduction in those on placebo. Virtually all the decline in NTx in response to alendronate occurred by month 3. The difference between the treatment groups for the bone formation marker BSAP (serum bone-specific alkaline phosphatase) was also significant after 2 years ($p<0.001$), with 38% mean decrease in BSAP in men taking alendronate compared with a 5% reduction in those on placebo.

Table 3 summarizes the tolerability results of the study. A total of 205 men had at least one clinical adverse experience: 124 men (84.9%) on alendronate and 81 men (85.3%) on placebo. There were no statistically significant differences ($p>0.05$) between the treatment groups with regard to the proportion of patients with drug-related adverse effects, serious adverse effects, and adverse effects of the cardiovascular and digestive systems. The proportion of men who discontinued from the study due to an adverse effect was significantly higher ($p=0.02$) in those on placebo (11% [n=10]) than alendronate (3.0% [n=4]). The frequency of any adverse upper gastrointestinal (GI) effects in those taking alendronate (25%) or placebo (22%) was similar between the groups despite the concomitant use of nonsteroidal anti-inflammatory drugs reported in 41% of those taking alendronate and 36% of those taking placebo.

Table 3. Alendronate for the Treatment of Osteoporosis in Men: Incidence of Adverse Effects

Adverse Effects	Alendronate (n=146)	Placebo (n=95)
Drug-related adverse effects*	17%	14%
Serious adverse effects	18%	23%
Cardiovascular system	16%	17%
Digestive system	35%	39%
Any upper GI event	25%	22%
Abdominal pain	8%	4%
Acid regurgitation	5%	5%
Esophagitis	1%	1%
Dyspepsia	6%	1%

*Determined by the investigator to be possibly, probably, or definitely drug-related.

The authors concluded that alendronate was generally well tolerated in this study and significantly increased spine, hip, and total body BMD, along with reducing vertebral fractures and preventing decreases in height in men with osteoporosis.

Selected Findings

The following are selected findings from the pivotal clinical trial that evaluated the efficacy and tolerability of alendronate 10 mg once daily for 2 years in men with osteoporosis:

- Alendronate increased lumbar spine BMD (primary endpoint) regardless of age, femoral neck T-score, prevalent vertebral fractures, or gonadal status.
- At all sites measured, the increases in BMD in men taking alendronate were significantly greater than those on placebo ($p<0.001$ for all comparisons).
- The magnitude of the effects of alendronate on BMD was similar to that observed in postmenopausal women after 2 years of treatment.
- The reduction in the incidence of vertebral fractures in men treated with alendronate compared with placebo was consistent with the reduction in vertebral fractures noted with alendronate therapy in postmenopausal women.
- Treatment with alendronate prevented decreases of height in men with osteoporosis compared with those on placebo.
- Biochemical markers of bone turnover (urinary NTx, BSAP) were significantly decreased in men taking alendronate compared with placebo.
- Alendronate was generally well tolerated in this study and few men withdrew from the study because of an adverse effect.

Questions

1. **What percentage of hip fractures occurs in men worldwide?**
   a. 5% to 10%
   b. 10% to 15%
   c. 15% to 20%
   d. 20% to 25%
   e. 25% to 30%

2. **As seen in women, vertebral fracture in men is associated with which of the following?**
   a. Increased height
   b. Kyphosis
   c. Decreased risk of other fractures
   d. Decreased disability
   e. All of the above

3. **When does the incidence of limb fractures (mainly lower limb fractures) related to trauma begin to increase in men due to osteoporosis?**
   a. At age 55
   b. At age 65
   c. Before age 75
   d. After age 75

4. **True / False: The following risk factors may predispose men to osteoporotic fractures: low BMD, low body mass, advancing age, smoking, excessive alcohol intake, physical inactivity, and increased tendency for falls (for hip fractures).**

5. **Which of the following statements explains why men are less predisposed to have fragile bones than women?**
   a. Men have greater peak bone mass and larger cross-sectional bone surface.
   b. Men have less trabecular bone loss.
   c. Men experience trabecular bone loss by trabecular thinning rather than by trabecular perforation.
   d. Men have less cortical bone thinning.
   e. All of the above

6. **Changes in bone mass in men has been reported to be affected by which of the following factors?**
   a. Aging
   b. Sex steroids (androgens)
   c. A and B
   d. None of the above

7. **True / False: Primary osteoporosis (which includes idiopathic and age-related forms) and hypogonadism together account for about 20% of all cases of osteoporosis in men, whereas glucocorticoid-induced osteoporosis accounts for about 60% of all cases of osteoporosis in men.**

8. **Based on data available to date, what is the relationship of bone mass to fracture risk in men?**
   a. Decreases in bone mass increases fracture risk
   b. Increases in bone mass increases fracture risk
   c. Decreases in bone mass decreases fracture risk
   d. None of the above

9. **Similar to women, BMD determinations in men can be used for which of the following?**
   a. Diagnosing low bone mass
   b. Gauging the severity of bone loss
   c. Serving as a baseline to judge the progression or improvement of disease
   d. All of the above

10. **Which of the following statements regarding the efficacy of alendronate 10 mg once daily in men with osteoporosis are true?**
    a. At all sites measured, the increases in BMD in men taking alendronate were significantly greater than those on placebo ($p<0.001$ for all comparisons).
    b. The incidence of vertebral fractures was lower in men taking alendronate compared with placebo (0.8% vs. 7.1%, $p=0.02$), as noted by quantitative methods.
    c. Men taking alendronate had a 0.6 mm decrease in height compared with a decrease of 2.4 mm in those on placebo ($p=0.02$ for the difference between groups).
    d. Biochemical markers of bone turnover (urinary NTx, BSAP) were significantly decreased in men taking alendronate compared with placebo.
    e. All of the above

Answers

1. e
2. b
3. d
4. true
5. e
6. c
7. false
8. a
9. d
10. e

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