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Risk factors for male osteoporosis

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Abstract

Hypogonadism from long-term androgen deprivation therapy (ADT), either by bilateral orchiectomy or administration of gonadotropin-releasing hormone (GnRH) agonists, causes significant and accelerated bone loss that may increase the risk of bone fractures in men with prostate cancer. Recent reports, as well as new data from our institution, have shown a high prevalence of pre-existing osteopenia and osteoporosis in men with prostate cancer before receiving ADT, and this is of great concern because of the risk of further bone loss during ADT. Data from these studies suggest the urgent need for clinical guidelines for screening, prevention, and treatment of these cases. This article reviews the prevalence and risk factors associated with osteoporosis in men and addresses risk factors in men with prostate cancer not receiving ADT. Considerations for the patient selection and timing of bone densitometry will also be discussed.

Keywords: Androgen deprivation therapy; Prostate cancer; Osteoporosis; Orchiectomy; Gonadotropin-releasing hormone agonists

Introduction

Androgen deprivation therapy (ADT), either by bilateral orchiectomy or administration of gonadotropin-releasing hormone (GnRH) agonists, remains the mainstay of therapy for patients with advanced prostate cancer. Its use is rapidly increasing with the inclusion of patients with prostate specific antigen (PSA) recurrence or biochemical relapse following definitive therapy for primary treatment of locally advanced prostate cancer. With more aggressive PSA screening, many men initiating ADT are younger and asymptomatic, and are now faced with the long-term use of ADT. Retrospective and prospective studies have consistently shown that hypogonadism from ADT results in significant bone loss and higher incidence of bone fractures in men with prostate cancer than seen in controls [1–9]. Further, reports have also shown a high prevalence of pre-existing osteopenia and osteoporosis in men with prostate cancer before receiving ADT [5,7,8].

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Definition of osteoporosis

Osteoporosis is a disease characterized by low bone mineral density (BMD) resulting in increased susceptibility to bone fractures [10]. Osteoporosis is responsible for more than 1.5 million fractures that occur in the United States each year. Over 250,000 fractures involve the hip, and it is estimated that 20 percent of men with osteoporotic hip fractures will die within one year from a complication of the injury [11]. Osteoporotic fractures are expected to rise dramatically over the next 50 years as the population continues to age and life expectancy increases [12].

The burden of osteoporosis is largely because of hip and vertebral fractures [13]. In 1990, an estimated 30% of 1.7 million hip fractures occurred in men worldwide [14]. Men have a higher mortality after hip fracture than do women [14]. Osteoporosis can often cause pain, diminished quality of life, decreased physical mobility and independence, inability to work, and increased burden on caregivers who must care for the patient with fracture. Furthermore, in 1995, the National Osteoporosis Foundation estimated that direct care of patients in the United States with osteoporosis to be $10 to 20 billion annually.

Studies have shown that reduction in BMD is the most important predictor of osteoporotic fractures in both men and women [15,16]. Accordingly, the World Health Organization has defined normal, osteopenia, osteoporosis, and

established osteoporosis in women based on BMD as compared to young adult mean values [17]. Normal BMD is defined as T-score value > -1 standard deviation (SD), osteopenia as T-score between -1 and -2.5 SD, osteoporosis as T-score < -2.5 SD, and established osteoporosis as T-score < -2.5 SD below the young adult mean value in the presence of one or more fractures. While these definitions are based on women, they are also used to diagnose osteopenia and osteoporosis in men.

Risk factors for osteoporosis in men

Hypogonadism is a well-established risk factor of osteoporosis in men [18]. Other risk factors include aging, ethnicity, smoking, excessive alcohol consumption, deficiency in dietary calcium intake, physical inactivity or sedentary lifestyle, low body mass index (BMI), certain diseases, and medications, particularly chronic use of glucocorticoid agents.

Aging

During childhood and adolescence, more bone is formed than resorbed. Peak bone mass is reached in the twenties and is maintained up to the age of 40 for both men and women. After age 40, bone mass begins to decrease at the rate of about 0.4 to 1.3% per year in the peripheral skeleton of men and women up to age 80. By the age of 80, it is estimated that bone mass declines to half its maximum value [19].

Age-related reductions in the number of Leydig cells and testosterone levels are associated with bone loss in elderly men [14]. An estimated 5-fold increased risk of hip fractures was seen among elderly men with age-related hypogonadism [20]. Among elderly men admitted for spinal osteoporosis, approximately 5% of the cases were a result of hypogonadism [21].

Ethnicity

On the average, African-Americans have approximately 10% greater BMD than Whites in the United States [22]. Asians have lower BMD when compared with Caucasians. However, after controlling for body size, these differences are reduced, and the variability of BMD within each race is much greater than the differences between races [23].

Smoking

Although the exact mechanism is not clearly understood, cigarette smoking is a risk factor for osteoporosis. Vogel and colleagues (1997) examined bone density and bone loss rates among 1303 Japanese-American men who were current cigarette smokers, past smokers, and nonsmokers [24]. Results indicated that compared with never smokers, current and past smokers had significantly less bone density, especially in the cancellous calcaneus and trabecular distal radius. Also, the magnitude of the smoking effect was strongly associated with the duration of smoking. These findings were consistent with the Rotterdam study in which a statistically significant higher rate of bone loss was seen in both elderly men and women who currently smoked cigarettes [16].

Alcohol consumption

Moderate alcohol intake is associated with lower risk of fracture [25]. However, excessive alcohol consumption is associated with low BMD and increased fracture risk among men and women. Possible mechanisms include impaired calcium metabolism secondary to liver disease and increased risk for falls because of poor balance [15].

Dietary calcium level

Adequate intake of calcium is necessary for achieving optimal peak bone mass during development and maintaining calcium homeostasis [15,18]. Calcium deficiency increases bone resorption and is a common cause of accelerated bone loss in the elderly. In a population-based study involving 1,856 elderly men in Rotterdam, Netherlands between 1990 through 1995, after adjusting for age, BMI, lower limb disability, energy intake, cigarette smoking, and alcohol consumption, higher calcium intake was associated with lower rates of bone loss in men ($P = 0.04$) [16].

Both American men and women consume less than 800 mg of calcium per day [26]. Currently, the National Institute of Health recommends for men over the age of 63 years old to have a calcium intake of 1500 mg/day to prevent osteoporosis [27]. This calcium requirement can be achieved by the addition of calcium supplements (such calcium carbonate, calcium citrate, and calcium phosphate) with dietary calcium intake. In a 3 year prospective, randomized, double-blind trial, daily intake of 500 mg of calcium with 700 IU of vitamin D supplements has been shown to significantly increase BMD and reduce the incidence of fractures as compared to placebo in both elderly men and women aged 65 years or older [28].

Physical activity

Physical activity plays an important role in achieving peak bone mass during adolescence and is positively associated with BMD in adult males [18,29]. Nguyen et al. [18] examined the efficacy of multiple risk factors for osteoporotic fractures in 820 men aged 60 years or older. They found that higher physical activity was protective against fracture risk. Similar results were reported by Kujala et al. [30] and Kanis et al. [31]. Physical exercise, particularly weight bearing exercise, may prevent fractures from falls [32]. While the exact exercise prescription for both men and

women is currently unknown, benefits of exercise include increasing bone density, muscle strength, balance, and coordination.

BMI

BMI is positively related to BMD [33]. Studies have shown that lower BMI scores were associated with BMD loss [16,34,35]. As well, increasing BMI is associated with a reduced risk of fracture in men [25,36]. Studies also suggest that obesity is associated with increased BMD and may decrease incidence of fracture in men.

Diseases and medications

Diseases, such as chronic renal failure, hyperparathyroidism, hyperthyroidism, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), and functional loss associated with central nervous system disorders, are known to cause osteoporosis in men [18]. Glucocorticosteroids are extensively used by elderly as anti-inflammatory agents for treatment of acute and chronic asthma, chronic lung disease, and rheumatoid arthritis [37]. These medications, however, causes bone (particularly trabecular bone) loss through suppression of osteoblastic activity and inhibition of intestinal calcium absorption. Also, corticosteroid-related hypocalcemia directly stimulates PTH secretion, causing increased osteoclastic bone resorption. Risk factors associated with steroid-induced osteoporosis include total cumulative dose, daily dose of glucocoticoid, and duration of therapy [38]. Among 161 ambulatory patients with rheumatic disease treated with long-term prednisone, patients who were treated with a cumulative dose of less than 10 g of prednisone had an estimated 23% incidence of osteopenia and 22% incidence of fracture. Those who received 10 to 30 g had a 40% incidence of osteopenia and 33% incidence of fracture. Furthermore, patients who received over 30 g had 78% incidence of osteopenia and of those, 53% had radiographic evidence of fracture [39].

Histologic examination of bone among patients treated with long-term glucocorticoid therapy revealed an estimated 20% trabecular volume loss after 5 to 7 months of therapy. Also, 63% of individuals who received an average of 5 years of varying doses of glucocorticoid agents suffered significant bone loss [40].

Prevalence of osteopenia and osteoporosis before ADT

A number of studies have reported a high prevalence of osteopenia and osteoporosis in men before receiving ADT or on watchful waiting for their prostate cancer. The presence of osteopenia and osteoporosis before receiving ADT is of great concern because of the expected bone loss during long-term ADT, and therefore, these men may be at greater risk for developing osteoporotic fracture. Data on the factors associated with osteopenia and osteoporosis before ADT are limited and have not been well established. In a sample of 12 men (mean age of 78) with advanced prostate cancer, Diamond et al. [8] found 75% had osteoporosis in the lumbar spine and 33% had osteoporosis in the femoral neck before receiving ADT. Wei et al. [7] studied 8 men (median age = 76) with prostate cancer who were not on ADT and found 38% with osteopenia and 25% with osteoporosis. Risk factors for osteoporosis such as age, ethnicity, physical activity, smoking, alcohol consumption, and calcium levels were examined, but no significant differences were found between the ADT and no ADT groups [7]. Recently, in a sample of 35 men with a median age of 75, Berruti et al. [5] reported pre-existing osteopenia and osteoporosis in the lumbar spine (46% and 14%, respectively), and at the hip (40% and 4%, respectively). As well, no significant associations were found among age, physical activity, alcohol and caffeine consumption, calcium intake, and smoking habits with changes in BMD using univariate and multivariate regression analysis [5]. In our institution, we studied BMD of 34 men (mean age = 69) with nonmetastatic prostate cancer who have not received ADT, and we found 73.5% had osteopenia (55.9%) or osteoporosis (17.6%) of the lumbar spine and/or femur. In our sample, older age and lower BMI were factors significantly associated with bone loss in the lumbar spine and femur of these men.

When and for whom should bone mineral density be performed?

Currently, it remains unclear if and when bone densitometry should be obtained in men before, or while receiving ADT. For patients about to begin ADT, the urologist or caregiver needs to assess the risk factors for osteoporosis before initiating therapy. Given that ADT is known to cause a progressive decline in BMD and because osteoporosis is easier to prevent than to treat, men with significant risk factors should undergo BMD studies at baseline. Whether all men with prostate cancer should undergo BMD studies at baseline remains unclear. Our present practice is to only obtain baseline bone density studies in men with risk factors, and to wait 2 years while on ADT before obtaining bone density studies in men without risk factors given that men have a 30 percent higher peak bone mass than women [11,41]. At issue is whether merely the diagnosis of prostate cancer increases the risk for bone loss, and given the high incidence of low bone density in men with prostate cancer before receiving ADT [5,7,8], whether all these patients should have baseline bone density testing. Larger prospective studies will be required to resolve this issue.

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