



A comprehensive bone-health management approach for men with prostate cancer receiving androgen deprivation therapy

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ABSTRACT

For advanced and metastatic prostate cancer, androgen deprivation therapy (ADT) is the mainstay of treatment. Awareness of the potential bone-health complications consequent to ADT use is increasing. Many studies have shown that prolonged ADT leads to significant bone loss and increased fracture risk that negatively affect quality of life. Clinical practice guidelines for preserving bone health in men with prostate cancer on ADT vary across Canada. This paper reviews recent studies on bone health in men with prostate cancer receiving ADT and the current evidence regarding bone-health monitoring and management in reference to Canadian provincial guidelines. Based on this narrative review, we provide general bone-health management recommendations for men with prostate cancer receiving ADT.

KEY WORDS

Prostate cancer, androgen deprivation therapy, osteoporosis, bone, fracture

1. INTRODUCTION

Androgen deprivation therapy (ADT), achieved by bilateral orchiectomy or administration of luteinizing-hormone releasing-hormone agonists, is the mainstay of treatment for advanced prostate cancer. Use of ADT can improve survival in men with locally advanced prostate cancer^{1,2}, but its prolonged use can lead to significant bone loss that may affect health-related quality of life in these men. Bone loss in men who are receiving ADT is not a trivial issue. More than 70% of men with prostate cancer are older than 65 and already at risk for osteoporosis or fragility fracture^{3,4}. In this article, we review recent studies on bone health in men with prostate cancer receiving ADT and current evidence concerning bone-health monitoring and management in reference to Canadian provincial guidelines.

2. OSTEOPOROSIS AND FRACTURE RISK IN MEN WITH PROSTATE CANCER RECEIVING ADT

Serum testosterone and estrogen fall to subnormal levels during ADT. These hormones are important for maintaining bone mass because they exert anti-apoptotic effects on osteoblasts and osteocytes and pro-apoptotic effects on osteoclasts⁵. Men with nonmetastatic prostate cancer receiving continuous or intermittent ADT can have significant bone mineral density (BMD) loss as early as the first 6–12 months after starting ADT^{6,7}. Men who receive continuous ADT experience bone loss of up to 10% over 2 years⁸ and clinically significant annual BMD decrements of –1.4% to –4.6% at the lumbar spine, –0.6% to –3.3% at the total hip, and –0.7% to –3.9% at the femoral neck⁹.

Intermittent administration appears to attenuate the negative impact of ADT on bone, because the overall odds ratio for having osteoporosis is significantly higher in men on continuous ADT [odds ratio (OR): 2.14; $p = 0.032$] than in those on intermittent ADT¹⁰. Longer duration of continuous ADT was associated with a greater loss in BMD, but the long-term effects of intermittent ADT on BMD are not known⁹. The results of a number of large randomized trials of intermittent ADT are anticipated in the near future and may well shed further light on this question.

The risk of fracture also increases with ADT. Two Canadian population-based cohort studies examined the effect of ADT on fracture risk in men with prostate cancer^{11,12}. In Manitoba, the adjusted ORs for fracture risk with current and past use of ADT were 1.71 [95% confidence interval (CI): 1.13 to 2.58] and 2.42 (95% CI: 1.42 to 4.12) respectively¹¹. Similar results were noted for secondary fracture outcome in the Ontario study: ADT users had an adjusted hazard ratio of 1.65 (95% CI: 1.53 to 1.77)¹². Two large U.S. cohort studies also demonstrated a similar effect of ADT on the risk of fracture in men with prostate cancer^{13,14}. Significantly more fractures occurred in men with prostate cancer who received ADT (19.4%)

than in those who did not (12.5%, $p < 0.001$)¹³. Men with prostate cancer who received ADT had increased relative risks for fracture—1.76 for hip and 1.18 for vertebrae—compared with those who did not¹⁴. Taken together, the foregoing findings indicate that ADT significantly increases the risk of fracture in men with prostate cancer and that ADT-related bone health is an important health issue.

3. MONITORING BONE HEALTH IN MEN WITH PROSTATE CANCER RECEIVING ADT

3.1 BMD

Although evidence of increased fracture risk in men with prostate cancer on ADT is mounting, baseline and follow-up BMD testing are not routine in Canada¹⁵. It would be prudent to establish a standardized clinical practice guideline for assessing men before the initiation of, and during, ADT. The bone densitometry definition of osteoporosis in men is not as well standardized as it is in postmenopausal women because BMD is less frequently measured in men than in women¹⁶. Nonetheless, BMD measurements are equally useful for predicting fractures in men and in women (Table 1)^{17,18}.

Dual-energy X-ray absorptiometry (DXA) is the most widely used test for measuring BMD and the methodology adopted by the World Health Organization (WHO) as the reference standard for the diagnosis of osteoporosis. Other technologies—such as quantitative computed tomography, peripheral radiography, quantitative ultrasound, and magnetic resonance imaging—can provide insights into bone strength and structure, but are primarily used in research and cannot be used for the diagnosis of osteoporosis under the WHO criteria; they therefore have no defined clinical role in Canada at the present time^{19–22}. To define osteoporosis in men age 50 years or older, the WHO recommends using the same classification of BMD (based on the T score system, with the number of standard deviations that BMD measured by DXA is above- or below-average for a young white female

reference population) as that used in women²³. A DXA T score of the lumbar spine, femoral neck, or total hip less than or equal to -2.5 is consistent with osteoporosis; a T score between -1.0 and -2.5 is considered low bone mass (osteopenia)²³. Osteoporosis Canada recommends BMD testing for all men older than 65 and for younger men with clinical risk factors for fracture, including the use of high-risk medications such as ADT²⁴.

Standardized clinical practice guidelines on BMD testing for men with prostate cancer receiving ADT are lacking in Canada. Osteoporosis Canada recommends that men on ADT be assessed for fracture risk and be considered for osteoporosis therapy to prevent fractures²⁴. However, current practice varies across Canada: existing guidelines range from the specific to the general, and in most provinces, no guidelines have been established (Table II). For instance, the Alberta Health Services recommends specific time periods for DXA scans: at baseline for all patients undergoing long-term ADT of more than 6 months, with follow-up at 12 months for those with normal BMD at baseline and at 6 months for those with osteopenia at baseline²⁵. The BC Cancer Agency recommends DXA if ADT will be used for more than 6 months (adjuvant or palliative), with the following general time periods for follow-up DXA scans: every 24 months for men with prostate cancer on ADT, or every 18 months if additional risk factors for rapid BMD loss are present²⁶. Cancer Care Nova Scotia recommends that patients be screened with DXA scans²⁸. There are no specific published BMD testing guidelines in Manitoba, Ontario, Quebec, Saskatchewan, or the remaining provinces and territories.

3.2 Fracture Risk Assessment Tools

Besides BMD testing, assessment tools that can help to better assess fracture risk based on other clinical factors are available. The WHO Fracture Risk Assessment Tool, FRAX (visit www.shef.ac.uk/FRAX/), can be used to estimate the 10-year probabilities of a hip fracture and a major osteoporosis-related fracture by

TABLE 1 World Health Organization diagnostic categories for osteopenia and osteoporosis based on bone mass measurements¹⁷

Category	Bone mass
Normal	A value for bone mineral density (BMD) within 1.0 standard deviation (SD) of the young adult female reference mean (T score ≥ -1 SD).
Low bone mass (osteopenia)	A value for BMD more than 1.0 but less than 2.5 standard deviations below the young adult female reference mean (T score < -1 and > -2.5 SD).
Osteoporosis	A value for BMD 2.5 or more standard deviations below the young adult female reference mean (T score ≤ -2.5 SD).
Severe osteoporosis (established)	A value for BMD more than 2.5 standard deviations below the young adult female reference mean (T score > -2.5 SD) in the presence of one or more fragility fractures.

TABLE II Canadian provincial bone management guidelines in men with prostate cancer receiving androgen deprivation therapy (ADT)

Provincial organization	Recommendations in the published bone management guideline
Alberta Health Services ²⁵	<p>Baseline dual-energy X-ray absorptiometry for all patients going on long-term (>6 months) ADT.</p> <ul style="list-style-type: none"> For patients with osteoporosis (T score < -2.5), bisphosphonate therapy should be initiated. For patients with osteopenia (T score -1 to -2.5), repeat bone mineral density test every 6 months (high risk) or every 12 months (low risk). For T score greater than 1, repeat bone mineral density test every 12 months (high risk) or 24 months (low risk). <p>Calcium 1500 mg and vitamin D 800 IU daily for all men on ADT.</p>
BC Cancer Agency ^{26,27}	<p>Bone mineral density test every 2 years; men with other risk factors that may accelerate bone loss or in whom baseline osteopenia is detected, 18-month follow-up bone mineral density tests may be justified.</p> <p>Exercise, particularly weight-bearing exercise. (Care must be taken to tailor any exercise in men with established osteoporosis or older men at risk of falls). Total daily dietary and supplemental calcium intake 1500 mg.</p> <p>Vitamin D3 at 800 IU daily.</p>
Cancer Care Nova Scotia ²⁸	<p>Patients should be screened using dual-energy X-ray absorptiometry.</p> <ul style="list-style-type: none"> If osteoporosis is present, consider bisphosphonate. <p>Patients should be encouraged to take vitamin D and calcium supplements.</p>
Saskatchewan Cancer Agency ²⁹	All patients require adequate calcium and vitamin D intake, using supplements if necessary.

taking into account clinical factors including sex, age, body mass index, prior fracture, parental hip fracture, prolonged corticosteroid use, rheumatoid arthritis (or secondary causes of osteoporosis, including ADT), current smoking, alcohol intake (3 or more units daily), and femoral neck BMD status^{30,31}. Each FRAX tool is calibrated for use in a specific country, based on fracture data from that country. The Canadian FRAX tool was recently made available after direct independent validation of its performance in fracture-risk stratification³². Osteoporosis Canada has updated its clinical practice guidelines to incorporate the Canadian FRAX tool into the management paradigm²⁴. The Canadian Association of Radiologists and Osteoporosis Canada have also updated a simplified semiquantitative system, CAROC, for 10-year fracture risk stratification in routine clinical practice; it is based on the Canadian FRAX tool²⁴. With either the Canadian FRAX tool or CAROC, an individual's 10-year major osteoporotic fracture risk is stratified into three zones designated low-risk (less than 10%), moderate risk (10%–20%), and high risk (exceeding 20%). Treatment should be considered if the risk of major osteoporotic fracture over 10 years exceeds 20% (among other indications for treatment). Although not validated in the ADT population, these tools assess fracture risk better than BMD alone can, and they can help to inform clinical decision-making in connection with BMD testing and treatment for Canadian men receiving ADT^{24,30,32–34}.

4. MANAGEMENT OF BONE HEALTH IN MEN WITH PROSTATE CANCER RECEIVING ADT

Bone-health management for men with prostate cancer receiving ADT varies across Canada. Some published osteoporosis management guidelines are available in Canada, but there is a need to establish standardized, evidence-based bone health management guidelines for men receiving ADT across Canada. The challenge is to determine easily accessible interventions that can maintain BMD or reduce bone loss and prevent ADT-related fractures. Lifestyle modification and pharmacologic interventions are potential strategies, but few provincial guidelines have been established with regard to men with prostate cancer receiving ADT (Table II).

4.1 Lifestyle Modification

4.1.1 Smoking and Alcohol Use

Smoking and excessive alcohol use are considered primary risk factors for fracture in older men. Smoking is consistently associated with bone loss in older men³⁵. The risk of bone loss is particularly high in those who are current and moderate-to-heavy smokers (>20 pack-years) with low body weight (<75 kg)³⁶. In fact, smoking cessation has a favourable effect on bone health^{37,38}. Alcohol use has a dose-dependent association with bone loss. Excessive alcohol use is associated with increased bone

loss^{39,40}. Alcohol use has also been found to have a significant effect on BMD in men with prostate cancer on ADT⁴¹. As a general rule, smoking and excessive alcohol consumption should be avoided.

4.1.2 Exercise

The increase in fracture risk in men with prostate cancer receiving ADT likely results from a combination of BMD reduction and sarcopenia, which is another side effect of ADT. Loss of lean muscle mass leads, in the lower extremities, to poor muscle strength and poor physical function, both of which are major risk factors for falls and fractures^{42–45}. Declining or low physical activity is associated with an increased risk of fracture in older men^{46,47}, likely mediated by reduction in physical function and BMD. Older men with low physical activity levels have poor physical function⁴⁸. Poor physical function (such as impairment in rising, walking, and balance tasks) is consistently associated with low BMD, bone loss³⁵, and hip fractures⁴⁵. Men with prostate cancer receiving ADT should therefore be strongly encouraged to maintain bone health, muscle strength, and physical function through an active lifestyle.

Active lifestyle through exercise should be an essential component in the management of bone health for men with prostate cancer starting ADT. Exercise with sufficient bone-loading force such as repetitive weight-bearing aerobic (walking, aerobics) and resistance training are effective in improving BMD in the general adult population, with a pooled positive effect of 1.8% (95% CI: 0.6% to 3.0%) at the spine⁴⁹. The effectiveness of weight-bearing exercise on BMD is also seen in adults at risk of osteoporosis. Postmenopausal women 45 years of age and older who perform repetitive weight-bearing exercises have significant increases in hip BMD of $3.5\% \pm 0.8\%$ ⁵⁰ and weighted mean differences for spinal BMD of 1.79 (95% CI: 0.58 to 3.01)⁵¹. Older adults 50 years of age and older with chronic stroke or low BMD are able to maintain hip BMD through weight-bearing exercise^{52,53}. A systematic review found that healthy men 40 years of age and older who are physically active through moderate-to-vigorous weight-bearing exercise (such as walking) have a reduction of 45% (95% CI: 31% to 56%) in hip fracture risk⁵⁴.

The benefits of weight-bearing aerobic or resistance exercise on BMD would likely be seen in men on ADT who are willing and able to participate. Exercise programs that include aerobic^{55,56} and resistance training^{56–58} have already demonstrated beneficial effects on quality of life, fatigue, lean muscle mass, muscle strength, physical function, and balance in men with prostate cancer. Specifically, muscle strength, physical function, and balance are important factors that have positive effects on BMD⁵² and fall prevention^{45,46} in older men. It has not yet been determined whether exercise can improve BMD and prevent fragility fractures in men with prostate cancer receiving ADT.

Currently, no exercise guidelines have been established for the prevention of secondary osteoporosis in men with prostate cancer on ADT. Based on current evidence for the positive effects of physical activity on BMD, fall-related risks (muscle strength, physical function, and balance), and fracture prevention in older adults, the general physical activity recommendations in *Canada's Physical Activity Guide to Healthy Active Living for Older Adults*⁵³ are relevant and should be recommended to men with prostate cancer on ADT who do not have osteoporosis (Table III). The guideline recommends a target daily cumulative duration of 30–60 minutes of moderate physical activity most days of the week, aiming for 10 minutes of activity at a time and progressively building in time and intensity based on the individual's ability. In particular, weight-bearing aerobic, strengthening, and balance activities may be beneficial for bone health in men with prostate cancer on ADT.

Currently, no published studies have reported on whether exercise therapy prevents BMD loss in men with prostate cancer receiving ADT who already have osteoporosis. Exercise recommendations for men with osteoporosis receiving ADT should follow the 2010 Canadian clinical practice guidelines for osteoporosis management (Table III)²⁴. The guideline encourages men with osteoporosis—or those at risk for osteoporosis—to participate in weight-bearing aerobic exercise or resistance training (or both) appropriate to individual's age and functional capacity (grade B). The guideline also recommends that those at risk of falls engage in exercises that promote balance—for example, tai chi or balance and gait training (grade A). For those who have had vertebral fractures, core stability exercises to improve core muscle strength and posture are recommended (grade B). Exercise frequency, duration, and intensity were not included in the guidelines, but should follow individual recommendations based on multidisciplinary bone health management team assessments.

4.2 Pharmacologic Interventions

4.2.1 Calcium and Vitamin D Supplementation

Calcium and vitamin D are necessary for normal skeletal homeostasis. Vitamin D promotes intestinal absorption of calcium and phosphorus. Skeletal muscle contains vitamin D receptors, and supplementation may improve muscle strength and function in the lower extremities⁵⁹. However, it is common for men with prostate cancer to have inadequate vitamin D and calcium intake^{60–62}.

Vitamin D alone, or vitamin D in combination with calcium, has been shown to be beneficial with respect to BMD and fall and fracture prevention in older men and women^{63–73}. A meta-analysis concluded that vitamin D supplementation with at least 700 IU daily reduced the risk of a fall by more than

TABLE III Exercise intervention recommendations for men receiving androgen deprivation therapy

<i>Without osteoporosis^a</i>	<i>With osteoporosis^b</i>
Daily cumulative duration of 30–60 minutes of moderate physical activity most days of the week:	Those with osteoporosis or at risk for osteoporosis:
<ul style="list-style-type: none"> • Minimum 10 minutes of activity at a time • Progressive increase in time and intensity based on the individual's ability 	<ul style="list-style-type: none"> • Weight-bearing aerobic exercises or resistance training (or both) appropriate for the individual's age and functional capacity
Specific exercises that could benefit bone health:	Those at risk of falls:
<ul style="list-style-type: none"> • Weight-bearing aerobic activities (for example, walking, cycling, hiking, dancing) 4–7 days per week 	<ul style="list-style-type: none"> • Exercises that promote balance (for example, tai chi) or balance and gait training
AND	Those who have had vertebral fractures:
<ul style="list-style-type: none"> • Strength and balance activities (for example, weight training, stair climbing, wall push-ups, chair rise exercise) 2–4 days per week 	<ul style="list-style-type: none"> • Core stability exercises to improve core muscle strength and posture
	Exercise frequency, duration, and intensity should be based on individual recommendations from the multidisciplinary bone health management team assessments.

^a Based on *Canada's Physical Activity Guide to Healthy Active Living for Older Adults*⁵³.

^b Based on the 2010 Canadian Medical Association consensus statement on the management of osteoporosis²⁴.

20% in both community and institutionalized elderly people⁷³. Another meta-analysis showed that the benefit of vitamin D in fracture prevention is dose-dependent⁷⁴. A daily vitamin D dose of 800 IU reduced the relative risk of hip (RR: 0.82; 95% CI: 0.69 to 0.97) and non-vertebral fracture (RR: 0.80; 95% CI: 0.72 to 0.89) for individuals 65 years of age and older, but no significant fracture benefit was observed with low-dose vitamin D therapy (400 IU daily)⁷⁴.

The recently released Osteoporosis Canada evidence-based guideline on vitamin D recommends a daily intake of at least 800 IU in men and women over the age of 50 to reduce the risk of osteoporosis and the same 800 IU in those who already have osteoporosis⁵⁹. Daily intake of vitamin D up to 2000 IU is considered safe. To achieve optimal vitamin D status, some people require a daily vitamin D intake above 2000 IU; however, intake at that level should proceed only under medical supervision, with monitoring to exclude the rare occurrence of vitamin D toxicity⁵⁹.

For men with osteoporosis who are receiving ADT, measurement of serum 25-hydroxyvitamin D should be considered after 3–4 months of adequate supplementation; the measurement should not be repeated if an optimal level is achieved. Osteoporosis Canada does not recommend routine measurement of serum 25-hydroxyvitamin D in people without osteoporosis or in those with conditions affecting vitamin D absorption or action.

A meta-analysis demonstrated that calcium in combination with vitamin D significantly reduced the occurrence of fractures⁷⁵. Daily calcium doses of at least 1200 mg in combination with vitamin D reduces the all-fracture RR by 20% (RR: 0.80; 95% CI: 0.72 to 0.89) for people 50 years of age and older, which is significantly more beneficial than a daily calcium dose below 1200 mg⁷⁵. Although the

tolerable upper limit for daily calcium intake from all sources (diet and supplements) is 2500 mg⁷⁶, calcium supplements exceeding 1200 mg daily often cause gastrointestinal symptoms such as constipation, which limit compliance. Therefore, based on the evidence, daily calcium intake from all sources (diet and supplements) of 1200 mg and vitamin D supplementation of 800–2000 IU should be recommended for all men with prostate cancer on ADT to reduce the risk of osteoporosis and fractures (Table IV).

4.2.2 Bisphosphonates

Bisphosphonates inhibit osteoclast activity, thereby decreasing bone resorption. They are available in intravenous and oral formulations. Bisphosphonates are the class of medications most commonly used to treat osteoporosis in men. Although information about fracture prevention during ADT is limited, bisphosphonates have been shown to prevent ADT-related bone loss in men with prostate cancer^{77–80}.

A number of studies have investigated the effectiveness of intravenous and oral bisphosphonates in men with nonmetastatic prostate cancer receiving ADT. Intravenous bisphosphonates such as pamidronate 60 mg given every 12 weeks⁸⁰ or zoledronic acid 4 mg given every 3 months for 1 year^{79,81,82} prevented bone loss or increased BMD in men with prostate cancer newly initiated on ADT or having received up to 12 months of ADT. However, it is not clear if intravenous bisphosphonate is effective in preventing fractures.

The use of bisphosphonates to prevent ADT-induced bone loss or fracture is not yet recommended. Currently, zoledronic acid is used only to prevent skeletal-related events related to castration-resistant prostate cancer in men with bone metastases. A recent cost-effectiveness study of a oral bisphosphonate,

TABLE IV Recommendations for pharmacologic interventions in men receiving androgen deprivation therapy (ADT)

<i>Agent</i>	<i>Dose</i>	<i>Population</i>
Vitamin D ^{24,59}	800–2000 IU daily	All men receiving ADT
Calcium ^{24,59}	1200 mg daily oral intake from all sources	All men receiving ADT
First-line agents: ²⁴		
Alendronate	10 mg orally daily OR 70 mg orally weekly	Consider for treatment in the presence of <ul style="list-style-type: none">• prior low-trauma fractures (especially hip or vertebra) or more than 1 fragility fracture event• T score of –2.5 or less at the hip, spine, or distal third radius (after appropriate evaluation to exclude secondary causes)• high 10-year risk of major osteoporotic fracture—that is, exceeding 20% [men at moderate risk (10%–20%) may also benefit from treatment]
Risedronate	5 mg orally daily OR 35 mg orally weekly OR 75 mg on 2 consecutive days monthly OR 150 mg monthly	
Zoledronate	5 mg intravenously annually	
Denosumab	60 mg subcutaneously every 6 months	
Second-line agents:		
Etidronate	A cyclical oral dose of 400 mg daily for 2 weeks, every 3 months	
Nasal calcitonin	200 IU (1 activation) intranasally in 1 nostril once daily	

alendronate, commonly prescribed in fracture prevention, found that universal alendronate use without a BMD test was not justifiable in a hypothetical cohort of men 70 years of age receiving a 2-year course of ADT for locally advanced or high-risk localized prostate cancer⁸³. The comparison looked at 3 patient groups: no BMD test and no alendronate therapy; a BMD test before ADT, with selective alendronate therapy for 5 years in patients with osteoporosis; and universal alendronate therapy for 5 years without a baseline BMD test. Subject to the caveat that no direct current evidence from a clinical trial shows that alendronate actually reduces fracture risk in men with prostate cancer receiving ADT, the authors found that universal alendronate use is justifiable in men 80 years of age and older with a previous low-trauma fracture or with low BMD at baseline (femoral neck BMD more than 1.8 standard deviations below the reference mean) and that alendronate can be considered for men in whom a BMD test finds osteoporosis⁸³. In light of the earlier discussion, we do not currently recommend routine use of oral or intravenous bisphosphonate for fracture

prevention in men receiving ADT who do not have existing osteoporosis.

When men with prostate cancer are diagnosed with low BMD or osteoporosis, their management should follow the guidelines set out for men with osteoporosis. Osteoporosis Canada recommends that bisphosphonates (alendronate, risedronate, or zoledronic acid) be used as first-line therapy for the prevention of fractures in men with osteoporosis (grade D)²⁴. Oral bisphosphonates are generally well tolerated. The most common side effect is gastrointestinal upset; esophagitis or gastroesophageal ulceration are very occasionally seen. Alendronate (10 mg daily or 70 mg weekly) and risedronate (5 mg daily, 35 mg weekly, or 150 mg monthly) are recommended by Osteoporosis Canada as first-line therapy for osteoporosis²⁴. Zoledronic acid 5 mg intravenously once annually is also an effective first-line treatment²⁴. Etidronate is typically given in a cyclical dose of 400 mg daily for 2 weeks every 3 months as a second-line therapy for men with osteoporosis (Table IV)²⁴.

4.2.3 Denosumab

A recently approved parenteral agent, denosumab, holds promise for maintaining bone health and reducing fracture risk in men with nonmetastatic prostate cancer receiving ADT. Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor κ B ligand, the primary mediator of osteoclast differentiation and activation. A phase III randomized controlled multicentre trial of denosumab demonstrated that it increased BMD at all sites and reduced the incidence of new vertebral fractures among men receiving ADT for nonmetastatic prostate cancer⁸⁴. That study randomized more than 1400 men with nonmetastatic prostate cancer receiving ADT to receive either denosumab 60 mg subcutaneously every 6 months for 6 doses or placebo. At 24 months, BMD of the lumbar spine had increased by 5.6% in the denosumab group; the placebo group showed a loss of 1% ($p < 0.001$). Significant improvement in BMD at the total hip, femoral neck, and distal third of the radius was also observed in the denosumab group. Men who received denosumab had a lower incidence of new vertebral fractures at 36 months (1.5% vs. 3.9% with placebo). Rates of adverse events were similar in both groups, but one report suggests that denosumab may increase the risk of cellulitis⁸⁵.

4.2.4 Calcitonin

Salmon calcitonin is a peptide hormone that inhibits bone resorption. Calcitonin is considered a second-line option for treating men with osteoporosis who are intolerant of other options (Table IV)²⁴. For osteoporosis treatment, the nasal formulation of calcitonin is preferred to the injectable formulation because of fewer side effects. Minor side effects include nasal irritation, epistaxis, and other nasal symptoms.

4.2.5 Selective Estrogen Receptor Modulators

A few selective estrogen receptor modulators (SERMs) have been tested in men receiving ADT for prostate cancer. Raloxifene and toremifene, second-generation oral SERMs, have both demonstrated beneficial effects on bone health in men with nonmetastatic prostate cancer receiving ADT. In a 12-month open-label randomized controlled trial of 48 men with nonmetastatic prostate cancer on ADT, those who received raloxifene experienced significant increases in total hip BMD ($p < 0.001$)⁸⁶. In a recent 2-year phase III randomized placebo-controlled trial of 646 men with nonmetastatic prostate cancer receiving ADT, toremifene demonstrated more promising results⁸⁷. Those who received toremifene experienced a significant increase in BMD at the lumbar spine, hip, and femoral neck ($p < 0.001$) and also a significantly lower incidence of new vertebral fractures (2.5% vs. 4.9% with placebo, $p < 0.05$). However, SERMs are not currently approved for the treatment or prevention of osteoporosis in men receiving ADT.

5. CONCLUSIONS AND RECOMMENDATIONS

Maintenance of bone health is a critical issue in the treatment of men with prostate cancer receiving ADT. These men are at high risk of developing bone loss and fractures. Evidence-based guidelines to manage bone health in the context of ADT are lacking. Based on the recommendations from Osteoporosis Canada, we suggest baseline measurement of BMD at the initiation of ADT, with periodic reassessment during therapy depending on the initial findings. Although not validated in the ADT population, the Canadian FRAX tool or CAROC is recommended to assess 10-year fracture risk and to guide pharmacologic intervention. No consensus has yet emerged on optimal calcium and vitamin D intakes in men with prostate cancer on ADT. Daily intake of 1200 mg elemental calcium from all sources and supplementation with 800–2000 IU vitamin D daily is generally suggested based on risk and serum level of vitamin D, as recommended by Osteoporosis Canada. Men with prostate cancer receiving ADT should engage in regular weight-bearing aerobic, strengthening, and balance exercises. Further studies are needed to define the optimal exercise regimen and the roles of bisphosphonates, denosumab, and SERMs in improving bone health in this population.

6. CONFLICT OF INTEREST DISCLOSURES

WDL has been an advisory board member for Amgen, Genzyme, and Novartis; has received unrestricted research grants from Amgen, Genzyme, Merck Frosst, Procter and Gamble, and Sanofi–Aventis; has received speaker's fees from Amgen and Merck Frosst; and has received travel funds for activities unrelated to this paper from Genzyme. YKJL received a speaker's fee from Amgen. No conflict of interest declared for CEL, PC, JG, and MG.

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