Citation: BoneKEy Reports **4**, Article number: 716 (2015) | doi:10.1038/bonekey.2015.85

www.nature.com/bonekey

REVIEW

Androgen-deprivation therapy and bone loss in prostate cancer patients: a clinical review

Marc Bienz[1] and Fred Saad[2]

[1]Faculty of Medicine, University of Montreal, Montreal, Canada. [2]Department of Urology, University of Montreal Hospital Center, Montreal, Canada.

Androgen-deprivation therapy (ADT) has become a standard of care in the management of advanced prostate cancer or as an adjunct therapy. However, ADT is associated with a well-known deleterious effect on bone health, resulting in a decrease in bone-mass density (BMD) and increased risk for fracture. With the longer life expectancy of prostate cancer patients, improvement of the quality of life has become increasingly important. Therefore, adequate screening, prevention and treatment of BMD loss is paramount. Zoledronic acid and denosumab have shown promising results in recent studies, which has led to the Food and Drug Administration approval of these treatment options in various settings throughout the course of the disease, including the prevention of ADT-associated bone loss. This review focuses on the various parameters that impact BMD loss in men initiating ADT, on the specific effect of ADT on bone health and on various lifestyle modifications and treatment options such as bisphosphonates, osteoclast-targeted therapy and selective estrogen-receptor modulators that have shown promising results in recent studies.

BoneKEy Reports **4**, Article number: 716 (2015) | doi:10.1038/bonekey.2015.85

Introduction

Prostate cancer (PCa) is the most common cancer among men.[1] Improvements in the screening and the management of the disease have led to earlier diagnosis and longer life expectancy of patients. Therefore, hence the multiple side effects associated with actual treatment options, the quality of life of these patients has become increasingly important.

In the natural course of the disease, despite local therapy, up to 40% of patients develop metastases, which have a high tropism for the bone. Bone metastasis contributes to mortality but is also the main cause of morbidity as they may result in skeletal-related events (SREs), which include fractures, spinal cord compressions and the need for bone surgery or radiation therapy as therapeutic or palliative measures.[2]

Thus, bone health is of important concern in patients with prostate cancer. Not only are patients diagnosed often predisposed to bone loss due in part to age, but most receive androgen-deprivation therapy (ADT). ADT is a standard of care for advanced disease that has also gained increasing importance as an adjunct therapy. It has been associated with a detrimental effect on bone health.[3] Bone loss in patients diagnosed with PCa and treated with ADT has become a highly raised topic. Bone loss remains an under-diagnosed and under-treated condition in those men and failure in proper screening and management may be detrimental to their quality of life. This manuscript will review key elements of bone health of patients undergoing ADT and give a comprehensive overview of current treatment options.

Key Components of Bone Metabolism in Men

Bone undergoes constant dynamic turnover and remodeling to adapt to mechanical stress and metabolism homeostasis under the regulation of osteoblasts, osteoclasts, hormones and other factors. Cortical bone is the hardest and densest type of osseous tissue that is designed to resist well to tensile stress, hence its predominance in long bones. It overlies bone marrow and trabecular bone (cancellous bone), a lighter form bone tissue of irregular and porous structure well suited to withstand compression. Therefore, trabecular bone is most frequently found in vertebrae and at the end of long bones. The inner surface of the cortex of the bone where significant bone resorption occurs is called the endosteum. In contrast, the periosteum on the outer membrane of cortical bone is the site of periosteal apposition, which results in bone enlargement (**Figure 1**).[4,5]

Correspondence: M Bienz, Faculty of Medicine, University of Montreal, 2900 Boulevard Edouard-Montpetit, Montreal H3T 1J4, Quebec, Canada.
E-mail: marc.bienz@gmail.com
or Dr F Saad, Department of Urology, Montreal University Hospital Center/Centre hospitalier universitaire de l'Université de Montréal (CHUM), 1058 Rue Saint-Denis, Montréal H2X 3J4, Quebec, Canada.
E-mail: fredsaad@umontreal.ca

Received 26 February 2015; accepted 8 May 2015; published online 24 June 2015

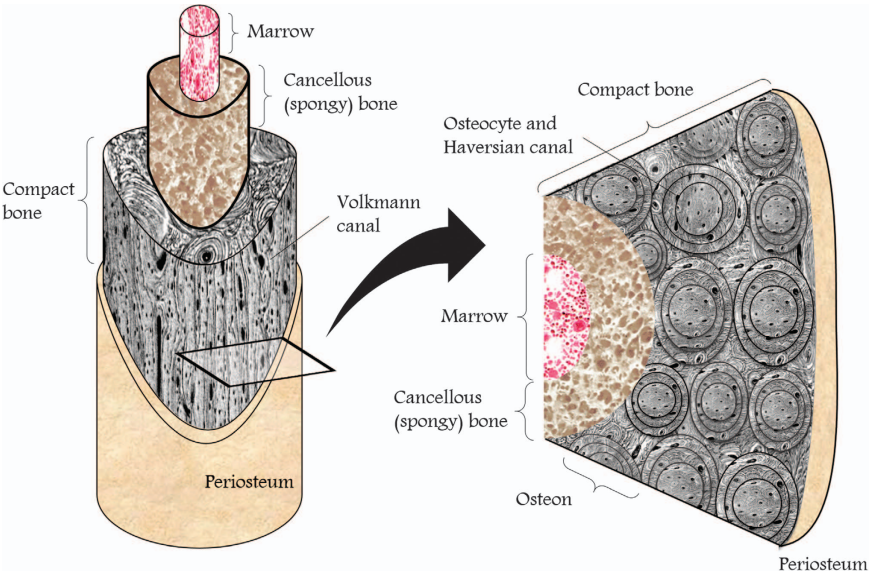

Figure 1 Identification of structures in a human long bone with a schematic representation of cortical and trabecular anatomy. On the left, the cortical bone surrounds the medullary canal in the center of the long bone. Near the end of the bone, at the epiphysis, trabecular bone (cancellous bone) is predominant. On the right, the magnified section of cortical bone illustrates the Haversian and Volkmann canals allowing oxygenation and communication between osteocytes. The osteon (the haversian system) formed of concentric rings of compact bone tissue gives structural support to cortical bone.[5]

Osteoblasts are the cellular units responsible of bone formation resulting in the apposition of calcium phosphate in the form of hydroxyapatite, which allows for the hardening of osseous connective tissue. As osteoblasts form bone, they encase themselves in their own matrix reaching their terminal differentiated state as osteocytes, now having a crucial role as mechano-sensory cells to maintain bone structure.[4] Osteoclasts are bone resorbing multinucleated cells of monocyte–marcrophage origin that secrete lytic enzymes and protons into a resorptive pit under their brush border. RANKL (receptor activator of nuclear factor-kB ligand) is a member of the tumor necrosis factor superfamily crucial for osteoclast activity. RANKL is expressed in a variety of cells including osteoblasts, T lymphocytes and stromal cells. It is a transmembrane protein that can undergo proteolytic cleavage by matrix metalloproteases. The cellular target of RANKL is RANK, a transmembrane receptor found on mature osteoclasts, the binding of which stimulates pathways responsible for the control of osteoclast differentiation, function and survival.[6]

Hormones also have a necessary role in bone homeostasis. In men, testosterone is converted to dihydrotestosterone, the most active trophic androgen in the prostate, via the 5-alpha reductase enzyme, and binds to the androgen receptor (AR) of osteoblasts of cortical and trabecular bone.[7] However, testosterone is also converted to estradiol via aromatase activity in peripheral tissues. Estradiol is the primary estrogen in men and is implicated in the remodeling of mainly trabecular bone via the estrogen receptor (ER). The ER is present in the cytosol of both the osteoblasts and osteoclasts.[8] Both the activated AR and ER interact with obsteoblast precursors to prevent osteoblast apoptosis, stimulate osteoclast apoptosis and decrease osteoclastogenesis.[7] This favors predominantly the increased formation of cortical bone by stimulating the lengthening of the epiphyseal growth plates and periosteal apposition. The continued growth of the periosteum during adult life in men increases the perimeter of their bones and partially offsets the normal endosteal bone loss caused by aging. Thus, men have wider bones compared with age-matched women.[7]

Quantitation of Bone Loss

Severe bone loss, known as osteoporosis, is characterized by compromised bone strength, which leads to a higher risk of fracture. Bone strength refers to two qualities of bone: quality and density. Bone quality cannot be readily assessed in a clinical setting but depends on qualifiable factors such as bone architecture, mineralization, accumulated discrete areas of damage and the quality of the collagen and minerals forming the bone's matrix.[9] Conversely, bone density is conventionally evaluated with a bone-mass density (BMD) measurement obtained through Dual-energy X-ray absorptiometry (DXA). However, DXA accounts for only 40% of the overall fracture risk for patients, the residual risk being associated with bone quality-associated factors. For the standardization of measurements, BMD is expressed as a *T*-score derived from comparing an individual's femoral neck BMD with that of a young-adult population of the same sex. Osteoporosis is diagnosed when the calculated *T*-score is $\geqslant$2.5 s.d. below the comparison BMD. However, by themselves, fragility fractures are sufficient for diagnosis of osteoporosis if trauma or cancer has been excluded.[10,11] Pre-osteoporotic low bone mass or osteopenia, which is at lower risk of fracture than osteoporosis, is considered to be within -1 to -2.5 s.d. Normal BMD values are within the -1 s.d. threshold.[12]

Low BMD measurements are directly related to increased fracture risk. Osteoporotic fractures are typically located on the vertebrae (27%), the distal radius named 'Colles fracture' (19%) and the femoral neck (14%). Although the hip fracture is not the most common site of injury, it is of high clinical relevance as of its association with severe comorbidity. In fact, post-hip

fracture death rates reach 30% within the first 6 months and even more so for men.[9] In addition, in men with low bone mass, studies have demonstrated that fractures are not uncommon even when the *T*-score does not reflect a need for treatment.[13] To improve fracture risk assessment, the World Health Organization has computed a FRAX algorithm that accounts for demographic risk factors, alcohol/tobacco/glucocorticoid use and other relevant past personal or familial history. The FRAX tool calculates the probability of risk for hip fracture and major osteoporotic fracture for the next 10 years.[10]

Clinical Predisposing Factors for Bone Loss and Osteoporosis

Considering factors that promote bone loss prior to ADT in PCa patients is important when initiating hormone therapy. The lifetime risk of bone fractures secondary to osteoporosis is $\sim$20%.[14] Cheung *et al.*[15] showed in an audit of 236 men that, at initiation of ADT, 11% had osteoporosis and 40% osteopenia. In addition, 61% of those with osteoporosis were unaware of it. These results reflect the need for a thorough screening of bone loss and its causes prior to initiation of ADT.

PCa is rarely diagnosed before the age of 40 ($<$1%), and aging in men is associated with multiple changes in bone strength.[16] With aging, the bone's resorption-formation ratio increases. Although periosteal circumference increases as described previously, cortical bone becomes thinner and more porous, endocortical bone becomes trabeculated and the width of the new and preexisting trabeculae decreases. These changes reduce the strength of the matrix and lowers BMD.[17] Sex hormones such as testosterone, but mostly estrogen, are potent inhibitors of bone resorption. With aging many changes occur. At the cellular level, oxidative stress, apoptosis and macroautophagy are some of the many mechanisms implicated in the altered remodeling process.[18] At the systemic level, the increase in sex hormone-binding globulin reduces the bioavailability of hormones, testicular Leydig cell mass and production of testosterone decrease, adrenal glands secrete less dehydroepiandrosterone, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) hormone production is altered, thus increasing the rate of bone loss in the elderly.[19] In addition, a physiological decrease in growth hormone (GH) secretion and pulsatility, together with a decreased insulin-like growth factor 1 (IGF-1) and IGF-binding-protein-3 hepatic production, negatively impacts bone health.[17] Chronic kidney disease may also participate in bone loss. In fact, it is considered to be causative for the rise of parathyroid hormone levels, vitamin D insufficiency and calcium malabsorption, all key elements of normal bone metabolism. Reduced mobility and protein intake in the elderly, together with the endocrine changes previously described such as reduced androgens and GH secretion, are associated with sarcopenia or the degenerative loss of skeletal muscle mass. Lower muscle mass reduces muscular loading and the production of bone-promoting factors from muscles.[17]

Osteoporosis promoted by other than age-related etiologies is referred to as secondary osteoporosis (**Table 1**). These include alcohol or glucocorticoid excess, vitamin D deficiency and hypogonadism. Primary hypogonadism results from disease of the testes, as a distinction from secondary hypogonadism, which refers to anomalies of hormones secreted at the pituitary or the hypothalamic level. Some drugs may lead to secondary hypogonadism such as chronic glucocorticoid or opiates use, gonadal steroids and GnRH analogs, the drug of choice for ADT for prostate cancer. Although no threshold has been defined, testosterone levels <150 ng dl^{-1} typically trigger hypogonadism-associated signs and symptoms.[7]

Finally, bone metastasis in hormone-naive patients can by themselves alter bone structure prior to the initiation of ADT. In fact, metastatic cancer cells stimulate the activation of osteoclasts and osteoblasts. The latter paradoxically increases the fragility of the bone, as in a tumor microenvironment misplaced and weaker woven bone is produced instead of a strong lamellar bone. The underlying osteolysis by the activation of osteoclasts further impacts the integrity of the mineral matrix resulting in bone pain and a higher risk for pathological fractures.[20,21]

Effect of Androgen Deprivation on Bone Metabolism in Men

The multiplication of available modalities of androgen-aimed therapies for prostate cancer has led ADT to become the mainstay for patients at various stages of the disease. However, reducing and maintaining testosterone to castrate levels results in a constellation of deleterious effects on health. These include reduced muscle mass, increased body fat, gynecomastia, diabetes, metabolic changes, cardiovascular events, sexual dysfunction, reduced penile/testis size, fatigue, hot flashes and reduced bone mass.[3] In ADT-mediated bone loss, both trabecular and cortical bone are affected, resulting in a decrease in BMD, especially in the first year after initiation of therapy.[22,23]

In fact, studies have shown that men undergoing ADT are four times more likely to develop significant bone deficiency.[24] In a large study of Shahinian *et al.*[24] of men surviving >5 years after diagnosis of prostate cancer, 19.4% of those who received ADT had a fracture compared with 12% in men who did not ($P<0.001$), and a significant relation was established between the number of doses of gonadotropin-releasing hormone given in the first 12 months and the risk of fracture. A list of studies

Table 1 Causes of osteoporosis in men

Causes related to modifiable lifestyle factors
Alcohol excess
Excessive exercise
Smoking
Causes related to nutritional deficiencies
Eating disorders
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

From Walsh and Eastell.[17]

reporting bone changes in men undergoing ADT is presented in **Table 2**. These results highlight the importance of androgens in bone health in men.

Interestingly, anti-androgens that prevent the activation of the androgen receptors, such as bicalutamide and enzalutamide, instead of reducing the production of androgens do not show a marked reduction in BMD with monotherapy in the most recent trials. However, this topic goes beyond the scope of this review.[25]

Monitoring BMD Loss in Men on ADT

Bone health management in patients undergoing ADT is critical in order to prevent bone loss-associated fractures. In fact, the population affected by PCa is prone to fractures due to the effects of ADT on bone health, the natural predisposition for low bone health related to aging with the continuing increase in life expectancy of patients, but also the risk of falling associated with cognitive disorders, fatigue and muscle weakness due to age and disease. Also, bone being the predominant site of metastases in prostate cancer, bone health is clinically relevant and hence the higher risk of SREs associated with bone metastasis. In this context, failure to properly screen patients is detrimental to the quality of life and life expectancy. Current osteoporosis screening recommendations for men from the World Health Organization, the American Association of Family Practitioners and the National Osteoporosis Foundation (NOF) recommend DXA in men above 70-year old. Men with risk factors should, however, be tested between the ages of 50- and 69-year old.[9]

An expert panel consensus on bone health and prostate cancer published in 2006 recommends a risk stratification of patients at the initiation of ADT. High-risk stratification includes one of the following risk factors: >6 months on ADT, previous fractures, a positive family history for osteoporosis, low body weight, smoking, excessive alcohol consumption, corticosteroid use, medical comorbidities and low vitamin D levels. Then, an initial baseline BMD should be assessed through DXA of the hip and/or DXA or quantitative computed tomography of the spine. Recommendations for low-risk patients with a normal *T*-score or osteopenia include a repeat BMD and a review of risk factors at 24 and 12 months, respectively. In patients considered high risk for bone loss, these evaluations should be performed at 12 and 6 months, respectively. In the case of a baseline *T*-score < -2.5 associated with osteoporosis, patients should initiate bisphosphonate treatment (view treatment section) and repeat bone health evaluation every 12 months.[26] Also, patients should be encouraged for lifestyle modifications such as cigarette and alcohol cessation, resistance-exercise training and assessing the need of supplementation daily calcium and vitamin D.

Management of Bone Loss During ADT

Lifestyle modification and oral supplementation

General measures for the management of osteoporosis in men include lifestyle modifications such as safe weight-bearing exercise,[27] moderate sun exposure, discouraged alcohol and smoking consumption and a balanced diet including calcium-rich foods.[28] In men undergoing ADT, supplementation

Table 2 Recent studies reporting bone changes in men undergoing ADT

References	*Design*	*Group characteristics*	*Bone health-associated outcome*
Basaria *et al*[41]	Cross-sectional	ADT group: 20 non-metastatic PCa men on GnRH agonists 12 months prior to study Non-ADT group: 18 age-matched non-metastatic PCa men without ADT Control group: 20 age-matched healthy men	Total body ($P=0.03$) and lumbar spine ($P<0.0001$) BMD was significantly lower in patients on ADT. ↑ urinary N-telopeptide in ADT group and the other groups ($P=0.02$) BMD inversely related to ADT duration
Berruti *et al.*[42]	Longitudinal	35 men with non-metastatic PCa under LHRH for 12 months	Baseline: 40% osteopenic, 4% osteoporotic at the hip Significant BMD decrease post-ADT at the lumbar spine ($P<0.002$) and the hip ($P<0.03$)
Preston *et al.*[43]	Longitudinal case-control	ADT group: 39 PCa patients Control group: 39 healthy men	Significant lower BMD for distal forearm ($P<0.0005$), femoral neck ($P=0.0018$), trochanter ($P=0.0019$) in ADT arm compared with control group
Greenspan *et al*[44]	Longitudinal case-control	Acute ADT group: 30 men on <6 months ADT Chronic ADT group: 50 men on $\geqslant 6$ months ADT Non-ADT group: 72 men not on ADT Control group: 43 healty age-matched controls	Acute ADT group was associated with elevated markers of bone formation and resorption after 6 and 12 months ($P<0.05$) Significant lower BMD for total hip, the trochanter, the total radius, total body and posteroanterior spind (all $P<0.05$) in the acute ADT group Significant lower BMD at the total radius in the chronic ADT group ($P<0.05$)
Galvao *et al.*[45]	Longitudinal	72 men with non-metastatic PCa under ADT for 36 weeks	Significant decrease for hip, spine, whole-body and upper limb BMD ($P<0.001$)
Galvao *et al*[46]	Longitudinal	ADT group: 48 men on ADT for PCa Control group: 70 healthy age-matched controls	Lower total body BMD ($P=0.013$), upper limb BMD ($P=0.002$), lower limb BMD ($P=0.013$) and total hip BMD ($P=0.034$) in ADT patients compared with control
Ziaran *et al.*[47]	Longitudinal case-control	ADT group: 95 men with locally advanced non-metastatic PCa on long-term ADT (24 months) Control group: 88 age- and BMI-matched controls	At 24 months, a significant lumber spine ($P=0.001$), total hip ($P<0.022$) and femoral neck ($P=0.037$) BMD difference was observed between groups

Abbreviations: ADT, androgen-deprivation therapy; BMD, bone-mass density; BMI, body mass index; LHRH, luteinizing hormone-releasing hormone; PCa, prostate cancer.

of calcium and vitamin D should be considered and especially in men avoiding milk products, who have intestinal malabsorption, or in house-bound men such as those residing in homes for the elderly.[28] Recommendations from the NOF for all men >50 years old and reasonably for all men on ADT include at least 1200 mg calcium daily from the diet and supplements and supplemental vitamin D at doses of 800–1000 IU per day.[3,29] In fact, most studies on bisphosphonates in the management of bone loss included supplementation for all participants.[22] Fall prevention should also be of concern. Such strategies include evaluating vision, hearing and neurological problems, reviewing prescription for side effects that could promote imbalance and reducing the risk of falling.[29]

Bisphosphonates

Bisphosphonates are pyrophosphate analogs, a normal component of bone matrix, that are actively deposited on hydroxyapatite by osteoblasts at sites of active bone metabolism. During osteoclast-mediated bone resorption, bisphosphonates are liberated and internalized by osteoclasts. The exact mechanism of action of bisphosphonates depends on their content of nitrogen, the presence of which has been associated with higher potency.

Non-nitrogen-containing bisphosphonates such as clodronate act as metabolized cytotoxic molecules in the osteoclast that causes loss of mitochondrial membrane potential and apoptosis.[30] Clodronate is an oral first-generation bisphosphonate. Two long-term survival trials showed a significantly better overall survival in the treatment arm for metastatic patients who started ADT. However, its effect on BMD was not evaluated.[31]

Nitrogen-containing bisphosphonates include pamidronate, alendronate, risendronate and zoledronic acid (**Table 3**). When internalized by the osteoclast, these compounds inhibit an enzyme, farnesyl diphosphonate synthase, resulting in an impairment of the osteoclast's ability to bind to the bone and additionally alters its capacity to maintain a brush border and produce proton, thus impairing the efficacy of its resorptive pit.[30] Among patients with non-metastatic PCa, pamidronate (60 mg intravenously (i.v.) every 12 weeks) combined to a leuprolide during a 48-week period was associated with a significantly higher BMD at the lumbar, tronchanter and the hip level as in the trabecular bone of the lumbar spine compared with patients receiving leuprolide alone.[32] However, pamidronate did not show an improvement of BMD compared with baseline value.

Zoledronic acid contains two nitrogen groups resulting in better potency. In fact, it is the most potent bisphosphonate in terms of farnesyl diphosphonate synthase and bone resorption inhibition.[30] In a double-blind randomized placebo-controlled trial, the BMD of non-metastatic prostate cancer patients undergoing ADT had increased at 1 year for all skeletal sites, which include the lumbar spine, femoral neck, trochanter and total hip in the treatment arm (4 mg zoledronic acid i.v. every 3 months). For the placebo group, all measurements showed a decrease in BMD at 1 year compared with baseline.[33] Similarly, in a randomized controlled trial, Michaelson *et al.*[34] evaluated the effect of a single dose of zoledronic acid (4 mg i.v.) on day 1 in patients with non-metastatic PCa receiving GnRH agonists with a *T*-score above -2.5. At 12 months, the treatment arm showed an increase posteroanterior lumbar spine BMD by $4.0 \pm 1.0\%$, resulting in a between-group difference of 7.1% (95% confidence interval (CI) 4.2–10.0, $P<0.001$). Increase in BMD under zoledronic acid was also observed at the total hip, the femoral neck and the trochanter, which resulted in significant between-group differences for the total hip and trochanter, respectively, at 2.6% (95% CI 0.9–4.3, $P=0.004$) and 3.1% (95% CI 0.9–5.3, $P=0.008$). Zoledronic acid also resulted in a significant decrease in serum N-telopeptide, a marker of osteoclast activity, compared with placebo with a between-group difference at 12 months of 27% (95% CI 6–48, $P=0.01$).[34] A summary of randomized placebo-controlled trials evaluating the use of zoledronic acid on BMD is reported in **Table 3**.

Denosumab

Denosumab is a human monoclonal RANKL antibody that acts by inhibiting the RANK–RANKL pathway, thus hindering osteoclast activity (**Table 3**). The efficacy of denosumab in patients undergoing ADT was demonstrated by the Denosumab HALT Prostate Cancer Study Group. In this study, men diagnosed with non-metastatic PCa undergoing ADT were assigned to either a 60 mg subcutaneous injection of denosumab or a placebo every 6 months. At 24 months, the treatment arm showed an increase in BMD at the total hip, the femoral neck, the distal third of radius and the whole body with a respective difference of 4.8, 3.9, 5.5 and 4.0% compared with placebo ($P \leqslant 0.001$ for all comparisons). The BMD of the placebo arm decreased at 24 months and was significantly lower than the treatment arm for all skeletal sites ($P \leqslant 0.001$). Moreover, this was the only study with enough power to show a reduced incidence of fractures in addition to the protective effect of denosumab on BMD. In fact, at 12, 24 and 36 months, the denosumab group had a significantly lower incidence of new vertebral fractures than the placebo group. At 36 months, the treatment arm had yielded a 62% (relative risk 0.38, 95% CI 0.19–0.78, $P=0.006$) reduction in the incidence of new vertebral fractures compared with placebo. Biochemical markers of bone turnover such as C-telopeptide, procollagen type 1 N-terminal peptide and TRAP-5b were also all significantly lower in the treatment arm at 36 months ($P \leqslant 0.001$).[35] This landmark study led to the US Food and Drug Administration approval of denosumab (commercialized as Prolia) in non-metastatic prostate cancer patients undergoing ADT as the only approved therapy to prevent hormone therapy-associated fractures.[36]

Selective estrogen-receptor modulators

Selective ER modulators (SERMs) have shown some promising results for BMD preservation in PCa for patients undergoing ADT. Raloxifene was first studied and was associated with an increase in BMD at the total hip and the trochanter ($P<0.001$) compared with placebo in a 12-month randomized trial of 48 men with non-metastatic PCa undergoing ADT.[37] Toremifene citrate is a second-generation SERM that acts as an estrogen-like agonist in bone and other specific tissues. In a double-blind, 24-month placebo-controlled phase III study, men receiving 80 mg of toremifene orally every day yielded a relative risk reduction in new vertebral fractures of 50% (95% CI -1.5–75.0, $P=0.05$) and significantly increased BMD at the lumbar spine, hip and femoral neck compared with placebo ($P \leqslant 0.001$). However, venous thromboembolic events were more frequently observed in the

Table 3 Summary of randomized-controlled trials evaluating bisphosphonates and denosumab to prevent bone loss in men with prostate cancer undergoing ADT

Authors (year)	*Study population*	*Study arms*	*Calcium/ Vitamin D*	*BMD change*
Oral bisphosphonates: alendronate, risedronate				
Greenspan *et al.*[48]	Non-metastatic PCa under ADT for <6 months, Total $n=112$	Group 1: Alendronate 70 mg weekly Group 2 Placebo	Yes	At 12 months, between-group differences: LS: 5.1% (95% CI 3.6–6.7, $P<0.001$) FN: 2.3% (95% CI 1.0–3.7, $P<0.001$)
Greenspan *et al.*[49]	Non-metastatic PCa under ADT in the past year	Group 1 ($n=23$) Alendronate 70 mg weekly after 1 year on the same regimen Group 2 ($n=25$): Placebo after 1 year on alendronate 70 mg weekly Group 3 ($n=48$) Alendronate 70 mg weekly after 1 year on placebo	Yes	At 24 months, between-group differences: Group 1–Group 2 Posteroanterior spine: $3.79\pm1.22\%$, $P=0.002$ Lateral spine: $4.97\pm2.13\%$, $P=0.021$ FN: $2.59\pm1.17\%$, $P=0.028$ TR: $0.67\pm0.99\%$, $P=0.500$ TH: $1.26\pm0.77\%$, $P=0.101$ Ultradistal radius: $2.34\pm0.98\%$, $P=0.018$ Total distal radius: $2.25\pm0.68\%$, $P=0.001$ Group 1–Group 3 Posteroanterior spine: $4.66\pm1.07\%$, $P<0.001$ Lateral spine: $4.64\pm1.98\%$, $P=0.02$ FN: $3.75\pm1.04\%$, $P<0.001$ TH: $1.92\pm0.68\%$, $P=0.005$ Ultradistal radius: 2.90 ± 0.86, $P<0.001$ Total distal radius: 2.07 ± 0.60, $P<0.001$ Group 2–Group 3 No significant difference
Taxel *et al.*[50]	Locally advanced PCa initiating ADT	Group 1 ($n=20$) Risedronate 35 mg weekly Group 2 ($n=20$) Placebo	Yes	At 6 months: FN: Group 1: no significant change, Group 2 -2.0, ($P<0.01$) TH: Group1: no significant change, Group 2 -2.2%, ($P<0.01$) LS: Group 1 $+1.7\%$, Group 2: no significant change
Klotz *et al*[51]	Localized PCa initiating leuprolide 30 mg IM q4 months	Group 1 ($n=84$) Alendronate 70 mg q1 week Group 2 ($n=102$) Placebo	Yes	At 12 months: LS: Group 1 $+1.7\%$, Group 2 -1.9% ($P<0.0001$) TH: Group 1 $+0.7\%$, Group 2 -1.6% ($P=0.631$) FN: Group 1 $+0.85\%$, Group 2 -0.56% ($P=0.032$)
Choo *et al.*[52]	Non-metastatic PCa undergoing radiation therapy and ADT	Group 1 ($n=52$) Risedronate 35 mg weekly for 2 years Group 2 ($n=52$) Placebo	Yes	At 12 months: FN: Group 1 $1.02\pm3.57\%$, Group 2 $-5.55\pm6.01\%$, $P=0.3517$ Proximal femur: Group 1 $8.09\pm3.97\%$, Group 2 $2.75\pm1.99\%$, $P=0.2394$ LS: Group 1 $-0.12\pm1.29\%$, Group 2 $-5.77\pm4.66\%$, $P=0.2485$ At 24 months: FN: Group 1 $-2.55\pm2.89\%$, Group 2 -5.56 ± 2.92, $P=0.467$ Proximal femur: Group 1 $9.81\pm3.07\%$, Group 2 $0.14\pm1.78\%$, $P=0.0096$ LS: Group 1 $-0.85\pm1.56\%$, Group 2 $-13.55\pm6.33\%$, $P=0.0583$
i.v. *Bisphosphonates: pamidronate and zoledronic acid*				
Smith *et al.*[53]	Non-metastatic advanced or recurrent PCa initiating leuprolide	Group 1 ($n=21$) Pamidronate 60 mg i.v. for 2 h q12 weeks Group 2 ($n=22$) Placebo	Yes	At 48 weeks, between-group differences: LS: 3.8% (95% CI 1.8–5.7, $P<0.001$) TR: 2.8% (95% CI 1.1–4.6, $P=0.003$) TH: 2.0% (95% CI 0.7–3.4, $P=0.005$) Trabecular bone (LS): 6.5% (95% CI 1.0–11.9, $P=0.02$)
Diamond *et al.*[54]	Metastatic PCa under GnRH agonist and androgen antagonist for <12 months Total $n=21$	Group 1 Pamidronate 90 mg i.v., single dose Group 2Placebo	No	At 6 months: LS: Group 1 $+7.8\pm1.5\%$, Group 2 $-5.7\pm1.6\%$, ($P=0.0001$) FN: Group 1 $+2.0\pm0.9\%$, Group 2 $-2.3\pm0.7\%$ ($P=0.0007$)
Smith *et al.*[33]	Non-metastatic PCa beginning ADT	Group 1 ($n=47$) Zoledronic acid 4 mg i.v. for 15 min q3 months Group 2 ($n=43$)	Yes	At 12 months, between-group differences: LS: 7.8% (95% CI 5.6–10.0, $P<0.001$) FN: 3.3% (95% CI 1.4–5.2, $P<0.001$) TR: 4.9% (95% CI 2.9–6.9, $P<0.001$) TH: 3.9% (95% CI 2.5–5.3, $P<0.001$) Nondominant forearm: 2.5%(95% CI -1.1 to 6.0, $P=0.17$)
Israeli *et al.*[55]	Non-metastatic PCa on ADT for <12 months	Group 1 ($n=112$) Zoledronic acid 4 mg i.v. over 15 min q3 months Group 2 ($n=110$) Placebo	Yes	At 52 weeks, between-group differences: LS: 6.7% (95% CI 5.4–8.0, $P<0.0001$) TH:3.7% (95% CI 2.8–4.7, $P<0.0001$)

Table 3 (Continued)

Authors (year)	*Study population*	*Study arms*	*Calcium/ Vitamin D*	*BMD change*
Michaelson *et al.*[56]	Non-metastatic PCa with a T-score > -2.5	Group 1 ($n=22$) Zoledronic acid 4 mg i.v., single dose on day 1 Group 2 ($n=22$) Placebo	Yes	At 12 months, between-group differences: LS: 7.1% (95% CI 4.2–10.0, $P<0.001$) TH: 2.6% (95% CI 0.9–4.3, $P=0.004$) FN: 2.1% (95% CI −0.1 to 4.4, $P=0.06$) TR: 3.1% (95% CI 0.9 − 5.3, $P=0.008$)
Ryan *et al.*[57]	Non-metastatic and metastatic PCa on ADT for < 12 months	Group 1 ($n=22$) Zoledronic acid 4 mg i.v. in 15 min Group 2 ($n=20$)Placebo	Calcium only	At 12 months, between-group differences: LS: 7.1% (95% CI 3.3–10.8, $P<0.001$) FN: 4.2% (95% CI 1.8–6.6, $P=0.001$)
Satoh *et al.*[58]	Metastatic hormone-naive PCa	Group 1 ($n=20$) Zoledronic acid 4 mg i.v. single dose on day 1 Group 2 ($n=20$) Placebo	No	At 12 months, between-group differences: Posteroanterior LS: 11.7% (95% CI 9.6–13.4, $P=0.0004$) TH: 5.7% (95% CI 4.6–6.9, $P=0.0008$) FN: 6.9% (95% CI 4.6–9.2, $P=0.0393$)
Bhoopalam *et al.*[59]	Non-metastatic PCa	STRATUM 1 (ADT < 1 year) Group 1 ($n=21$) Zoledronic acid 4 mg i.v. q3 months Group 2 ($n=23$) Placebo STRATUM 2 (ADT ⩾1 year) Group 1 ($n=21$) Zoledronic acid 4 mg i.v. q3 months Group 2 ($n=19$) Placebo	Yes	Stratum 1, at 12 months, between-group differences: LS: 8.25% (95% CI 2.96–13.54, $P=0.0029$) Right TH: 1.87% (95% CI 0.22–3.51, $P=0.005$) Left TH: 1.57% (95% CI −0.27 to 3.41, $P=0.031$) FN: non-significant bilaterally Stratum 2, at 12 months, between-group differences: LS: 3.83% (95% CI 1.48–6.07, $P=0.0013$) Right TH: non-significant Left TH: 2.16% (95% CI −0.26 to 4.59, $P=0.024$) FN: non-significant bilaterally
Casey *et al.*[60]	Non-metastatic PCa newly initiating ADT Total $n=200$	Group 1 Zoledronic acid 4 mg i.v. q3 months for 24 months Group 2 Placebo for 12 months followed by zoledronic acid 4 mg i.v. q3 months for 12 months Group 3 Placebo for 24 months	Yes	At 12 months, between-group differences: Group 1–Group 3 LS: 4.8%, $P<0.01$ TH: 2.9%, $P<0.01$ FN: 3.5%, $P<0.01$ At 24 months, between-group differences: Group 1–Group 3 LS: 5.3%, $P<0.05$ TH: 3.2%, $P<0.05$ FN: 3.4%, $P<0.05$ Group 2: BMD benefit, but insufficient to restore baseline BMD
Kapoor *et al.*[61]	Non-metastatic PCa with osteoporosis or osteopenia	Group 1 Zoledronic acid 4 mg i.v. q3 months Group 2 Placebo	Yes	At 12 months, between-group differences: LS: Group 1 7.93 ± 1.4%, Group 2 0.82 ± 1.7%, $P=0.003$ TH: Group 1 2.27 ± 0.92%, Group 2 0.71 ± 1.1, $P=0.271$ FN: Group 1 5.05 ± 1.04%, Group 2 −0.48 ± 1.4%, $P=0.009$
Denham *et al.*[62]	Locally advanced ADT-naive PCa	Group 1 ($n=268$) 6 months ADT Group 2 ($n=268$) 6 months ADT + 18 months zoledronic acid 4 mg i.v. q3 months Group 3 ($n=268$) 18 months ADT Group 4 ($n=267$) 18 months both ADT + zoledronic acid 4 mg i.v. q3 months	Yes	At 12 and 24 months analysis, receiving 18 months of zoledronic acid prevented BMD loss in groups 2 and 4.
RANKL antibody: denosumab				
Smith *et al.*[63]	PCa under ADT	Group 1 ($n=734$) Denosumab 60 mg s.c. q6 months Groups 2 ($n=734$) Placebo	Yes	At 24 months, between-group differences: LS: 6.7% ($P<0.001$) TH: 4.8% ($P\leqslant0.001$) FN: 3.9% ($P\leqslant0.001$) Distal third of radius: 5.5% ($P\leqslant0.001$) Whole body: 4.0% ($P\leqslant0.001$)

Abbreviations: ADT, androgen-deprivation therapy; BMD, bone mass density; CI, confidence interval; FN Femoral neck; i.v., intravenous; LS, lumbar spine; s.c., subcutaneous; TH, total hip; TR, trochanter.

treatment group compared with placebo (2.6% vs 1.1%), especially in patients over 80-year-old or who were immobilized.[38] A *post hoc* analysis of the efficacy and safety of toremifene in men younger than 80 years showed 79.5% decrease in relative risk of new vertebral fractures (95% CI 29.8–94.0, $P=0<0.005$), a significant increase in BMD at all measured skeletal sites ($P<0.001$) and similar rates of venous thromboembolic event compared with placebo (2.1% vs 1.0%, $P=0.26$).[39]

Current recommendations

For ADT-related bone loss, the National Comprehensive Cancer Network guidelines recommend calcium and vitamin D

supplementation with either 60 mg of denosumab subcutaneously every 6 months, 5 mg of zoledronic acid intravenously every year or 70 mg of alendronate orally every week in men for which the 10-year risk of hip fracture is $\geqslant$3% as calculated by the FRAX score.[3,40] For the prevention and treatment of other secondary causes of osteoporosis such as postmenopausal, male and glucocorticoid-induced osteoporosis, other drugs have been approved such as risedronate, ibandronate, raloxifene, calcitonin and teriparatide.[9]

Conclusion

Since the pioneer discovery of hormone depletion by bilateral orchiectomy in 1941 by Huggins and Hodges, androgen-deprivation therapy has evolved to become a cornerstone in prostate cancer treatment. With more effective treatment options, the survival of prostate cancer patients has increased considerably, thus raising concern for a better management of the quality of life. Therefore, bone health management has become a key topic for physicians as prostate cancer patients have been characterized with BMD loss, especially in the context of secondary osteoporosis associated with ADT, which adds a considerable burden on healthcare resources. Current bone-targeted therapies such as zoledronic acid and denosumab have become paramount in reducing bone fractures and bone pain in patients undergoing ADT treatment.

Conflict of Interest

FS is a consultant to and receives research funding from Amgen, Novartis and Bayer. The remaining author declares no conflict of interest.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277–300.
2. So A, Chin J, Fleshner N, Saad F. Management of skeletal-related events in patients with advanced prostate cancer and bone metastases: incorporating new agents into clinical practice. *Can Urol Assoc J* 2012; **6**: 465–470.
3. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL *et al.* Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2014; **67**: 825–836.
4. Datta HK, Ng WF, Walker JA, Tuck SP, Varanasi SS. The cell biology of bone metabolism. *J Clin Pathol* 2008; **61**: 577–587.
5. Haversian canal: Encyclopaedia Britannica Online; 2010 [cited 2015]. Merriam-Webster Inc: Available from: http://www.britannica.com/EBchecked/topic/72944/bone-marrow.
6. Boyce BF, Xing L. Biology of RANK, RANKL, and osteoprotegerin. *Arthritis Res Ther* 2007; **9**: S1.
7. Clarke BL, Khosla S. Androgens and bone. *Steroids* 2009; **74**: 296–305.
8. Gartrell BA, Saad F. Managing bone metastases and reducing skeletal related events in prostate cancer. *Nat Rev Clin Oncol* 2014; **11**: 335–345.
9. Nanes MS, Kallen CB. Osteoporosis. *Semin Nucl Med* 2014; **44**: 439–450.
10. James H 3rd, Aleksic I, Bienz MN, Pieczonka C, Iannotta P, Albala D *et al.* Comparison of fracture risk assessment tool score to bone mineral density for estimating fracture risk in patients with advanced prostate cancer on androgen deprivation therapy. *Urology* 2014; **84**: 164–168.
11. M K. Osteoporosis overview. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism* 2013, 345–347.
12. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporosis international* 1994; **4**: 368–381.
13. Seeman E, Bianchi G, Khosla S, Kanis JA, Orwoll E. Bone fragility in men–where are we? *Osteoporos Int* 2006; **17**: 1577–1583.
14. Saylor PJ, Morton RA, Hancock ML, Barnette KG, Steiner MS, Smith MR. Factors associated with vertebral fractures in men treated with androgen deprivation therapy for prostate cancer. *J Urol* 2011; **186**: 482–486.
15. Cheung AS, Pattison D, Bretherton I, Hoermann R, Lim Joon D, Ho E *et al.* Cardiovascular risk and bone loss in men undergoing androgen deprivation therapy for non-metastatic prostate cancer: implementation of standardized management guidelines. *Andrology* 2013; **1**: 583–589.
16. Saad F, McCormack M. Le cancer de la prostate, 3e édition. Éditeur AP, editor. Montreal 2012.
17. Walsh JS, Eastell R. Osteoporosis in men. *Nat Rev Endocrinol* 2013; **9**: 637–645.
18. Hendrickx G, Boudin E, Van Hul W. A look behind the scenes: the risk and pathogenesis of primary osteoporosis. *Nat Rev Rheumatol* (e-pub ahead of print 21 April 2015).
19. Qian SZ, Cheng XuY, Zhang J. Hormonal deficiency in elderly males. *Int J Androl* 2000; **23**: 1–3.
20. Israeli RS. Managing bone loss and bone metastases in prostate cancer patients: a focus on bisphosphonate therapy. *Rev Urol* 2008; **10**: 99–110.
21. Keller ET, Brown J. Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. *J Cell Biochem* 2004; **91**: 718–729.
22. Cheung AS, Zajac JD, Grossmann M. Muscle and bone effects of androgen deprivation therapy: current and emerging therapies. *Endocr Relat Cancer* 2014; **21**: R371–R394.
23. Hamilton EJ, Ghasem-Zadeh A, Gianatti E, Lim-Joon D, Bolton D, Zebaze R *et al.* Structural decay of bone microarchitecture in men with prostate cancer treated with androgen deprivation therapy. *J Clin Endocrinol Metab* 2010; **95**: E456–E463.
24. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005; **352**: 154–164.
25. Merseburger AS, Haas GP, von Klot CA. An update on enzalutamide in the treatment of prostate cancer. *Ther Adv Urol* 2015; **7**: 9–21.
26. Saad F, Higano CS, Sartor O, Colombel M, Murray R, Mason MD *et al.* The role of bisphosphonates in the treatment of prostate cancer: recommendations from an expert panel. *Clin Genitourin Cancer* 2006; **4**: 257–262.
27. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. *J Clin Oncol* 2014; **32**: 335–346.
28. Kaufman JM, Lapauw B, Goemaere S. Current and future treatments of osteoporosis in men. *Best Pract Res Clin Endocrinol Metabolism* 2014; **28**: 871–884.
29. Clinician's guide to prevention and treatment of osteoporosis: National Osteoporosis Foundation 2010.
30. Green JR. Bisphosphonates: preclinical review. *Oncologist* 2004; **9**: 3–13.
31. Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes MR. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. *Lancet Oncol* 2009; **10**: 872–876.
32. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA *et al.* Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001; **345**: 948–955.
33. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 2003; **169**: 2008–2012.
34. Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA *et al.* Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol* 2007; **25**: 1038–1042.
35. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F *et al.* Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009; **361**: 745–755.
36. El-Amm J, Freeman A, Patel N, Aragon-Ching JB. Bone-targeted therapies in metastatic castration-resistant prostate cancer: evolving paradigms. *Prostate Cancer* 2013; **2013**: 210686.
37. Smith MR, Fallon MA, Lee H, Finkelstein JS. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; **89**: 3841–3846.
38. Smith MR, Morton RA, Barnette KG, Sieber PR, Malkowicz SB, Rodriguez D *et al.* Toremifene to reduce fracture risk in men receiving androgen deprivation therapy for prostate cancer. *J Urol* 2010; **184**: 1316–1321.
39. Smith MR, Malkowicz SB, Brawer MK, Hancock ML, Morton RA, Steiner MS. Toremifene decreases vertebral fractures in men younger than 80 years receiving androgen deprivation therapy for prostate cancer. *J Urol* 2011; **186**: 2239–2244.
40. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar R *et al.* NCCN Task Force Report: bone health in cancer care. *J Natl Compr Canc Netw* 2013; **11**(Suppl 3):S1–S50.
41. Basaria S, Lieb J 2nd, Tang AM, DeWeese T, Carducci M, Eisenberger M *et al.* Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clin Endocrinol* 2002; **56**: 779–786.
42. Berruti A, Dogliotti L, Terrone C, Cerutti S, Isaia G, Tarabuzzi R *et al.* Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* 2002; **167**: 2361–2367.
43. Preston DM, Torrens JI, Harding P, Howard RS, Duncan WE, McLeod DG. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostatic Dis* 2002; **5**: 304–310.
44. Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* 2005; **90**: 6410–6417.
45. Galvao DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T *et al.* Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int* 2008; **102**: 44–47.
46. Galvao DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a

comprehensive cross-sectional investigation. *Prostate Cancer Prostatic Dis* 2009; **12**: 198–203.
47. Ziaran S, Goncalves FM, Sn JB. Complex metabolic and skeletal changes in men taking long-term androgen deprivation therapy. *Clin Genitourin Cancer* 2013; **11**: 33–38.
48. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Int Med* 2007; **146**: 416–424.
49. Greenspan SL, Nelson JB, Trump DL, Wagner JM, Miller ME, Perera S *et al.* Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy. *J Clin Oncol* 2008; **26**: 4426–4434.
50. Taxel P, Dowsett R, Richter L, Fall P, Klepinger A, Albertsen P. Risedronate prevents early bone loss and increased bone turnover in the first 6 months of luteinizing hormone-releasing hormone-agonist therapy for prostate cancer. *BJU Int* 2010; **106**: 1473–1476.
51. Klotz LH, McNeill IY, Kebabdjian M, Zhang L, Chin JL. A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: The Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) Study. *Eur Urol 2013; 63: 927–935.*
52. Choo R, Lukka H, Cheung P, Corbett T, Briones-Urbina R, Vieth R *et al.* Randomized, double-blinded, placebo-controlled, trial of risedronate for the prevention of bone mineral density loss in nonmetastatic prostate cancer patients receiving radiation therapy plus androgen deprivation therapy. *Int J Radiat Oncol Biol Phys* 2013; **85**: 1239–1245.
53. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA *et al.* Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001; **345**: 948–955.
54. Diamond TH, Winters J, Smith A, De Souza P, Kersley JH, Lynch WJ *et al.* The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study. *Cancer* 2001; **92**: 1444–1450.
55. Israeli RS, Rosenberg SJ, Saltzstein DR, Gottesman JE, Goldstein HR, Hull GW *et al.* The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. *Clin Genitourin Cancer* 2007; **5**: 271–277.
56. Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA *et al.* Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol* 2007; **25**: 1038–1042.
57. Ryan CW, Huo D, Bylow K, Demers LM, Stadler WM, Henderson TO *et al.* Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid. *BJU Int* 2007; **100**: 70–75.
58. Satoh T, Kimura M, Matsumoto K, Tabata K, Okusa H, Bessho H *et al.* Single infusion of zoledronic acid to prevent androgen deprivation therapy-induced bone loss in men with hormone-naive prostate carcinoma. *Cancer* 2009; **115**: 3468–3474.
59. Bhoopalam N, Campbell SC, Moritz T, Broderick WR, Iyer P, Arcenas AG *et al.* Intravenous zoledronic acid to prevent osteoporosis in a veteran population with multiple risk factors for bone loss on androgen deprivation therapy. *J Urol* 2009; **182**: 2257–2264.
60. Casey R, Gesztesi Z, Rochford J. Long term zoledronic acid during androgen blockade for prostate cancer. *Can J Urol* 2010; **17**: 5170–5177.
61. Kapoor A, Gupta A, Desai N, Ahn H. Effect of zoledronic Acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog. *Prostate Cancer* 2011; **2011**: 176164.
62. Denham JW, Nowitz M, Joseph D, Duchesne G, Spry NA, Lamb DS *et al.* Impact of androgen suppression and zoledronic acid on bone mineral density and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) randomized controlled trial for locally advanced prostate cancer. *BJU Int* 2014; **114**: 344–353.
63. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F *et al.* Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009; **361**: 745–755.