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REVIEW ARTICLE

Adverse effects of androgen deprivation therapy in patients with prostate cancer: Focus on muscle and bone health

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Summary

Androgen deprivation therapy (ADT) is the most effective systemic treatment for prostate cancer and can be succeeded either surgically or pharmaceutically. Both approaches lead to hypogonadism with a large variety of adverse events, including obesity, metabolic syndrome, osteoporosis, sarcopenia, diabetes mellitus, cardiovascular disease, gynecomastia and sexual dysfunction. In addition, undesirable effects on muscle and bone health may have a significant impact not only on the quality of life but also on life expectancy. Currently, supervised exercise seems to be the only intervention that could prevent the adverse effects of the ADT and improve quality of life. Lifestyle modification, supplementation of calcium, vitamin D and when indicated antiosteoporotic treatments improve bone health. However, patients receiving ADT must be well informed about the potential benefits as well as the risks of the treatment.

Key words: *androgen deprivation therapy, prostate cancer, sarcopenia, training, osteoporosis, fractures*

Introduction

Prostate cancer is the most common cancer and the second leading cause of cancer death in men [1,2]. Currently, due to an earlier diagnosis and improved treatments applied at any disease stage, patients with prostate cancer are living longer, but often with long-term treatment-related side effects that affect their quality of life (QoL) and their functional performance [3].

Androgen deprivation therapy (ADT) is the most effective systemic treatment for prostate cancer. It is estimated that 50% of men with prostate cancer will use ADT on their treatment course [4]. ADT improves disease-free and overall survival when administered in combination with external beam radiation therapy for localized and locally advanced disease [5,6] and enhances overall survival in nodal disease and is the mainstream treatment for metastatic disease [7-9].

ADT is succeeded either surgically with bilateral orchiectomy or pharmaceutically using GnRH agonists or antagonists and both approaches lead to hypogonadism [10-12]. Hypogonadism has a negative impact on lipid, glucose, muscle and bone metabolisms through decreases in testosterone levels, resulting in a large variety of adverse events, including obesity, metabolic syndrome, osteoporosis, sarcopenia, diabetes mellitus, cardiovascular disease, gynecomastia and sexual dysfunction. These undesirable effects may have a significant impact on health and QoL [13,14] and therefore the benefits of ADT for each patient must be weighed against treatment-related adverse effects. Bone and muscle

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health are a major issue in prostate cancer patients because impacts QoL duration [15].

The aim of this review was to focus on the adverse effects of ADT on the muscles and bones and to provide guidance for the prevention and treatment of these side effects. The effects of the newer hormonal treatments, such as abiraterone, enzalutamide and apalutamide, which have recently been introduced for the treatment of advanced prostate cancer, are not discussed in this review.

Effects of ADT on muscle

At present, the existing evidence suggests that chronic use of ADT in patients with prostate cancer can lead to muscle mass loss and that might result in a decrease of muscle strength, increased fragility, decline in the functional performance and loss of independence [16-18].

An age-related lean mass loss is known to occur in healthy adult men, at an average rate of 1-2% per year after the age of 40 and becomes more obvious after the fifth decade of life [19,20]. Moreover, at the same time, fat mass gradually increases until the age of seventy and then it stabilizes or slightly decreases [21]. ADT leads to a reduction of lean body mass and an increase of fat mass leading to "sarcopenic obesity'' [16,22-25]. These changes are consistent, are usually apparent after the first 3 months of treatment and are more prominent to older men [26]. Lean body mass reduction is between 1-4% and fat mass increase is about 10-20% within the first 12 months of ADT [27-31]. The decline in lean body mass is mainly from the upper and lower limbs and only minor changes occur in the trunk [32]. The fact that the trunk mainly has a large mass of non-contractile tissue explains the preferential loss from the limbs. Discontinuation of the ADT does not seem to reverse these changes [33].

Data on muscle strength and physical performance are less concordant. It seems though that muscle strength and endurance, in men on ADT for prostate cancer for variable duration, are declined within the first six months of treatment, mainly in the upper limbs, with less conclusive results for the lower limbs [34-39]. This deterioration in muscle strength could be partly explained by the reduction of lean mass but the increase of fatty infiltration (myosteatosis) of the skeletal muscle is also a contributing factor [40-42].

Recently, it has been reported that systemic ADT does not affect skeletal muscle loss uniformly. Compared with the control group, patients receiving ADT experienced marked reductions in levator ani volume, in the gluteus maximus, iliopsoas, and quadriceps, compared with the muscle volumes of the controls. In contrast, the changes between the two groups were not statistically significant for the gluteus medius and calf muscle volumes at 12 months of treatment. Finally, it has been reconfirmed that men receiving ADT had experienced significantly greater increases in intramuscular fat within the gluteus maximus compared with to the controls [43].

Potential mechanism of ADT on muscle

The exact mechanism by which ADT leads to all these changes in the skeletal muscle is not well understood, but it is considered to be multifactorial. Skeletal muscle mass is the result of a dynamic balance between signaling pathways that regulate muscle protein synthesis and degradation [44]. Thus, loss of muscle mass observed with ADT may be due to a decrease in protein synthesis, or an increase in protein degradation, or both, due to the low testosterone levels [34, 45]. Also, dysregulation of factors that activate anabolic pathways, such as the growth hormone/insulin-like growth factor-1 (GH/IGF1) and follistatin, and activation of factors such as myostatin, a potent negative regulator of muscle mass development, and ubiquitin ligases which regulate pathways that result in skeletal muscle degradation, might contribute to the observed changes [46].

Furthermore, it is possible that androgen deprivation may also affect other cell types within skeletal muscle, such as fibroblasts, blood vessels and motor neurons [47]. Fibroblasts have been implicated in the regulation of satellite cell activation and muscle regeneration [48]. Lastly, findings suggest that testosterone suppression can negatively impact the contractile properties of skeletal muscles by reducing Ca^{2+} sensitivity in both type I and type II fibers and reducing maximum specific force in type I fibers [49].

Treatment

Currently, there is strong evidence that exercise interventions conducted over 12–24 weeks consisting of two to three days per week were associated with significant improvements in health- and disease-specific QoL in men with PCa receiving ADT (Table 1) [50-57].

In regards to exercises, several studies have investigated the effect of different types of exercise on body composition changes. It has been found that resistance training can increase lean body mass [58,59], whereas aerobic exercise results in an insignificant increase [60,61]. Fat mass decrease

Table 1. Summary of more recent meta analysis and systematic review articles on the effects of training on muscles

First author	*Year*	*No. of studies included*	*Results*	*Ref*
Menichetti J	2016	17 (1989 pts)	Supervised resistance exercise produced evidence for benefits on quality of life.	50
Bourke L	2016	16 (1574 pts)	Exercise has moderate positive effect on quality of life, cancer-specific fatigue, submaximal fitness, and lower body strength. No evidence of benefit for disease progression, cardiovascular health, or sexual function.	51
Teleni L	2016	10 (708 pts)	Exercise enhances health and disease-specific QoL No effect on metabolic risk factors	52
Keilani M	2017	32 (1199 pts)	Exercise improves muscular strength, body composition and walk time	53
Yunfeng G	2017	15 (1135pts)	Exercise enhanced body strength, exercise tolerance, improve fatigue, ADT-caused obesity and Sexual function	54
Cormie P	2018		Exercise improved aerobic fitness, muscular strength, physical function, body composition, fatigue, sexual wellbeing, mental wellbeing, social function, comorbid disease risk factors, and quality of life.	55
Ying M	2018	11 (905 pts)	Exercise improved quality of life Exercise plus dietary advice could not significantly improve the QoL Lifestyle intervention could significantly change body composition but no obvious difference in mitigating fatigue and depression	56
Chen Z	2019	7(468 pts)	Muscle strength was improved significantly. No significant differences changes in lean mass	57

Table 2. Preventive strategies

Muscle health
Supervised resistant and aerobic exercises, 3-5 times/week for 12-24 weeks
Lifestyle modifications
Bone health
Supervised resistant exercises
Lifestyle modifications
Calcium and vitamin D supplementation
Bisphosphonates when needed
Denosumab when needed

in these patients has been observed with combination of both aerobic and resistance training exercise [62]. The most important finding is that the maximum success of these positive results is based on supervised exercise [63-65] (Table 2).

Exercise has also been linked with improvements in negative physiological changes associated with advanced cancer, such as cachexia. The extent to which this contributes to improve physical functioning and QoL is uncertain. Improvements in fatigue, lower limb function, and exercise capacity potentially occur due to well-established adaptations associated with exercise training, such as improvements in cardiac output, metabolic adaptations and recruitment of skeletal muscle motor units [66-69]. A substantive psychological benefit related to empowerment and self-efficacy could also be a factor [70].

In the effort to mitigate the adverse effects of ADT treatment on the muscle, novel pharmaceutical agents are being studied in early phase clinical trials. In this respect, treatments that target myokines and pre-inflammatory factors are under trial [71]. Also, selective androgen receptor modulators (SARMs) have been developed. They act as androgen agonists in muscle and bone but have a minimal androgenic activity on the prostate, skin and hair and currently preclinical data are encouraging [72].

Effects of the ADT on the bones

A decrease in bone density by approximately 0.5-1% per year is observed in healthy elderly men as part of normal aging. As most cases of prostate cancer occur in men aged 65 years or older, it is not surprising that 60-80% of ADT-naive patients have osteopenia or osteoporosis at diagnosis [73]. Thus, even in the absence of ADT, bone health is a concern in older men with prostate cancer. Prospective studies in prostate cancer patients receiving ADT have indicated that bone mass density (BMD) declines within months of the initiation of treatment, with a maximum decrease of 5-10% within the first year [74-76]. Bone turnover markers are also found to increase within the first 3-6 weeks of treatment [77]. Annual bone loss was found to be 2-8% for the lumbar spine and 1.8-6.5% for the femoral neck

and the reduction is persistent and similar for the different types of ADT [78-82]. With long-term ADT treatment, BMD continues to decline and osteoporosis is a very common treatment side effect in these patients [83-89]. A large study of men with prostate cancer on continuous long-term (>2 years) ADT showed that the prevalence of osteoporosis was 42.9%, 49.2%, 59.5%, 65.7% and 80.6% after 2, 3, 6, 8 and ≥ 10 years of ADT, respectively [90].

Novel techniques such as high-resolution peripheral quantitative computed tomography (HR-pQCT) and high-resolution magnetic resonance imaging (HR-MRI), that are able to assess cortical and trabecular microarchitecture, revealed that the distal radius is the site of greater decline both in cortical and trabecular bone and thus, with the greatest risk for fractures [91].

Epidemiological and retrospective studies have revealed that the risk for osteoporotic fractures in men on ADT is increased. Approximately 20% of men receiving ADT will have an osteoporotic fracture within the first five years of treatment. Age, race, geographic location, comorbidities and GnRH agonist treatment were independent prognostic risk factors and the presence of fracture was associated with more than twofold increase in the rate of death [92,93].

Potential mechanisms of ADT

To understand the mechanisms by which ADT causes bone damage is important to know the physiology of bone remodeling and the effects of sex steroids on bone metabolism. During the adult life a continuous bone remodeling occurs and BMD depends on the balance of cellular (osteoblasts-osteoclasts) and molecular (RANKL-osteoprotegerin etc.) processes. Alteration in the balance of these mechanisms may lead to reduced BMD and increased fracture risk [94]. Sex steroids play an important role in the regulation of bone remodeling. Testosterone exerts its effects on bone remodelling by stimulating the proliferation of osteoblasts and inhibiting apoptosis of osteoblasts and osteoclasts. In addition, testosterone affects the skeleton indirectly through its conversion by aromatase to estradiol. Estrogens are essential to the maintenance of bone mineral density, as they trigger the apoptosis of osteoclasts and decreases osteoblast's apoptosis. ADT, by reducing serum free testosterone levels to castrate range (<5% of the normal value) and serum estradiol levels to <30%, has become the most common contemporary cause of severe male hypogonadism [95]. Recent studies have demonstrated that if serum estradiol levels fall below a certain threshold, it creates an independent risk factor for fracture. Furthermore, changes in skeletal sensitivity to the bone-resorbing effects of parathyroid hormone might also contribute to ADT-induced BMD loss [96].

Treatment

In order to prevent the effects of ADT on bones, it is essential to identify patients who are at high risk for bone loss, which is quite challenging. Evaluation of baseline BMD, as it represents a major risk factor for fracture, should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT and should be repeated 12 months after treatment initiation with a subsequent individualized monitoring frequency [97]. The WHO FRAX tool is recommended for the evaluation of individual fracture risk but it has not been validated in these patients [98].

Lifestyle modification, including smoking cessation, decreased alcohol intake, normalization of BMI and exercise could be useful and are recommended [99]. Studies on the effect of exercise on bone metabolism in men on ADT are limited and in the majority of them BMD is a surrogate marker for fragility and not the end point for fracture risk. The existing data have indicated that regular physical activity in the form of weight-bearing exercise and resistance training, increases BMD and muscle strength and may decrease falls and thus fracture risk in these men [100,101].

Supplementation of Calcium (at least 1200 mg /day) and vitamin D (800 mg/day) is recommended by The National Institutes of Health Food and Nutrition Board for all men >50 years old, and seems reasonable for men with prostate cancer on ADT [102].

Various drugs have been evaluated for the management of ADT-induced osteopenia and osteoporosis [103]. In randomized trials bisphosphonates (alendronate, pamidronate and zoledronic acid) reduce loss or increase BMD in prostate cancer patients who receive ADT [104-106]. In a recent meta-analysis, a substantial effect in preventing fractures and osteoporosis was shown. In relation to fractures and osteoporosis, zoledronic acid showed the best number needed to treat (NTT), compared with placebo [107]. Denosumab is a human monoclonal antibody against RANKL (the receptor activator of nuclear factor-kB ligand), that blocks the maturation of pre-osteoclasts to osteoclasts. In a large randomized, placebo-controlled phase III trial that enrolled 1468 men receiving ADT and at high risk for fracture (history of fracture, age of 70 years or older, or low BMD), denosumab given subcutaneously every 6 months found to increase signifi-

cantly lumbar spine BMD at 24 months by 5.6% compared with a 1.0% loss in the placebo group. Similar results were seen in the total hip, femoral neck, and radius. In addition, denosumab led to a decreased incidence of new vertebral fractures at 3 year by 62%. The benefits were similar regardless the age, the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI [108].

In addition, two studies have shown that monotherapy with bicalutamide could be a bone-protective treatment, but suboptimal efficacy constitutes an important issue [109,110]. The intermittent androgen deprivation (IAD) might be associated with less bone impact, but further evidence is needed [111] (Table 2).

The selective estrogen receptor modulators (SERM) raloxifene and toremifene, although they are not currently approved by the US Food and Drug Administration (FDA) for the indication of preventing ADT-related bone loss, have been shown to significantly increase BMD in men on ADT. Raloxifene 60 mg/d, increased after 1 year the mean BMD of the total hip by 1.1% compared with a 2.6% loss in men not on raloxifene, while similar results were noticed in the femoral neck and trochanter [31]. In a phase III trial of 1284 prostate cancer men on ADT with a high fracture risk, toremifene significantly reduced fracture risk by 50% compared with placebo at 2 years, increased BMD at the lumbar spine, hip and femoral neck. However, venous thromboembolic events occurred more frequently in the toremifene group, especially in those aged > 80 years and in those who experienced prolonged immobilization [113,114].

Conclusion

Although it is well established that ADT could improve survival for men with prostate cancer under certain circumstances, it has also been shown that it can lead to a variety of potential harms. Given that muscle and bones are some of the most androgen-responsive organs, it is not surprising that ADT affects lean muscle mass, muscle strength and physical performance and predisposes to the loss of bone mineral density and increases the risk for osteoporotic fractures. The optimal management for these potential changes has not been defined yet, and further trials on this matter are required. Patients must be well informed about these risks and the potential benefits of therapy and ADT treatment should be given in patients with a proven survival benefit.

Conflict of interests

The authors declare no conflict of interests.

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