World Journal of Clinical Urology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5410/wjcu.v3.i3.227

World J Clin Urol 2014 November 24; 3(3): 227-237
ISSN 2219-2816 (online)

REVIEW

Functional and metabolic complications of androgen deprivation therapy

Jaime O Herrera-Caceres, Ricardo A Castillejos-Molina

Jaime O Herrera-Caceres, Ricardo A Castillejos-Molina, Department of Urology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Colonia Sección XVI, Delegación Tlalpan, México City 14000, México
Author contributions: Both authors collaborated equally in the design, acquisition of data and interpretation, writing and editing of the manuscript; both authors approve the final manuscript.
Correspondence to: Ricardo A Castillejos-Molina, MD, Department of Urology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Vasco de Quiroga 16, Colonia Sección XVI, Delegación Tlalpan, México City 14000, México. rcastillejosmolina@gmail.com
Telephone: +52-55-54870900 Fax: +52-55-54854380
Received: April 29, 2014 Revised: August 9, 2014
Accepted: September 6, 2014
Published online: November 24, 2014

Abstract

Prostate cancer is the most common non-cutaneous cancer in men worldwide. Several different treatment strategies are available including minimally invasive procedures for localized tumors such as radical prostatectomy, radiotherapy, and androgen deprivation therapy, among others. All these strategies can be given as mono-therapy or as combination therapy. For this review, we will focus on the side effects of androgen deprivation therapy, independent of the other treatment modalities. Some of the most common affections are loss of bone mineral density, weight gain and obesity, myocardial infarction and sudden death, metabolic syndrome and insulin resistance, dyslipidemia, loss of libido and erectile dysfunction, fatigue, cognitive decline, vasomotor flushing, to mention a few. All these alterations can have an impact on quality of life and even lead to more serious complications such as fractures and cardiovascular complications. We present recommendations for prevention, early recognition and treatment. The different modalities for androgen deprivation therapy have particular side-effects profiles and indications should be made in an individualized manner. Androgen deprivation therapy is a useful tool for some patients with prostate cancer but every effort should be made to avoid related complications. The use of guidelines and educational programs for both, patients and urologists, are extremely useful strategies.

Key words: Prostate cancer; Metabolic syndrome; Frailty syndrome; Complications; Sarcopeny; Androgen deprivation therapy

Core tip: The article will review the most common complications related to the androgen deprivation therapy. It includes the most relevant and up-to-date information, aiming to provide a reliable and concise review of the side effects of such therapy. Recommendations are made for the prevention, early detection and early treatment of patients.

Herrera-Caceres JO, Castillejos-Molina RA. Functional and metabolic complications of androgen deprivation therapy. *World J Clin Urol* 2014; 3(3): 227-237 Available from: URL: http://www.wjgnet.com/2219-2816/full/v3/i3/227.htm DOI: http://dx.doi.org/10.5410/wjcu.v3.i3.227

INTRODUCTION

Overall, the highest incidence of tumors is from the genital system (almost 338450 new cases expect to be diagnosed in 2013). Out of these, prostate cancer (PCa) is the most common accounting for more than 233000 new cases[1]. Anyhow, incidence of mortality from prostate cancer remains lower than that of lung cancer[1].

Patient prognosis depends widely on the risk classification[2]. With radical prostatectomy as the standard treatment for localized PCa, 5-year recurrence rates go from 6%-45%. Death rates from PCa also vary, going

from 65% survival at 5 years to a mortality of 1%-8% by year 10[3]. Considering these facts PCa can be considered a chronic disease, with chronic complications.

With an increasing survival expectancy, quality of life and functionality become a more relevant problem. In the general population, by age 70 about 20%-30% of patients present some form of disability [mobility, Instrumental or in activities of daily living (ADL)][4]. In patients with PCa, good oncologic outcome can be achieved with several treatment options. Each treatment modality has its own set of side effects that can interfere with patients' performance.

The following review will focus on the functional and metabolic complications that PCa patients develop during the follow-up of the disease.

EVIDENCE ACQUISITION

Original and review articles addressing complications of androgen deprivation therapy were obtained by a systematic search of PubMed. Keywords included "prostate cancer", "androgen deprivation therapy", "hormonal therapy", "frailty syndrome", "sarcopeny", "obesity", "osteoporosis", "metabolic syndrome", "arterial stiffness", "cardiovascular", "fatigue", "cognitive impairment", "loss of libido", "erectile dysfunction", "adverse effects" and "complications". We selected the most recent articles with a good level of evidence to be examined and included in our review. Prospective, randomized trials were prioritized. The review will focus on androgen deprivation therapy complications, in terms of related metabolic and functional impairment.

INTRODUCTION-ANDROGEN DEPRIVATION THERAPY

After the description of Huggins *et al*[5] about the hormonal dependency of PCa, androgen deprivation therapy (ADT) has been widely used for its treatment. There are several indications for ADT including metastatic and locally advanced tumors, concomitant administration with radiotherapy, recurrence treatment, primary treatment for localized tumors. It has also been proposed for all high-risk patients after radical prostatectomy[6,7]. Average survival of patients using ADT, with recurrence after primary treatment is 84 mo[8].

Physicians must be aware of the potential benefits and side effects associated to ADT. Such therapy should be used exclusively when there is a known benefit. The benefit must outweigh the affection in Quality of Life (QoL). Once the decision to start ADT is made, actions must be taken to reduce adverse side effects. Patients should start an exercise program[9]; early detection strategies and adequate treatments could improve outcomes.

In an interesting prospective randomized trial by Salonen *et al*[10], they treated patients with advanced PCa for 6 mo with goserelin acetate. After the initial 6 mo, patients were randomized to receive either continuous or intermittent ADT (given for at least 6 mo when PSA reached levels > 20 ng/mL). Adverse effects (cardiovascular complications and cardiovascular deaths, bone fractures and hot flushes) were similar among groups. Nevertheless, the primary outcome was QoL (activity limitation, physical activity and sexual function), which was significantly better in the group of intermittent therapy. Erectile dysfunction (ED) (15.7% *vs* 7.9%) and depressed mood (2.2% *vs* 0%) were more frequent in the intermitted ADT group. Hot flushes were the most frequent adverse events (47.1% *vs* 50.4%)[10]. Other studies have also shown a benefit of intermittent treatment in terms of QoL, fatigue, hot flashes, sexual desire and urinary symptoms in patients with biochemical recurrence after radiotherapy[11].

In a recent systematic review by Botrel *et al*[12] including 13 trials and 6419 patients under continuous or intermittent ADT, there was no benefit in overall QoL. Except for the presence of hot flushes and sexuality scores, there were no differences between the two treatment strategies. A benefit in survival could not be demonstrated[12]. A Cochrane Database Systematic Review obtained similar conclusions[13].

ADT can have several side effects including new onset diabetes mellitus, osteoporosis, decreased libido, ED, hot flushes, acute kidney injury and cognitive decline, among others[14]. These side effects can occur both with short- and long-term ADT[7]. For these reasons, urologists and oncologists should discuss the possible treatment strategies with the patients. The patient with PCa must be well aware of the possible complications before initializing either therapeutic option. They must know that even though intermittent ADT might have a slight benefit in terms of QoL or sexual function, such effects do not seem to last long, and there is no proven benefit in terms of survival[15,16]. Particularly concerning ADT, the patient must be aware that even though ADT may be regarded as a "non-invasive treatment" the side effects can be very deleterious and have a significant impact in QoL, or even life expectancy due to cardiovascular implications[17]. Urologists should consider the evidence based benefits and side effects before initiation of therapy[7].

The following review will focus on the adverse effects of ADT, as well as the management strategies of these complications. True benefits and complications should be analyzed before indicating ADT.

ANDROGEN DEFICIENCY IN THE AGING MALE

Testosterone deficiency is a common condition in aging men, with a decline rate of 0.8%/year in total testosterone levels. Such decline is greater after the age of 60 and in patients with chronic illness, including obesity[18]. Symptoms are non-specific and frequently go unrecognized. Several terms have been used for the condition encompassing a low testosterone level and compatible symptoms in a male patient, usually older than 40 years

old. The most accurate term is "Androgen Deficiency in the Aging Male" (ADAM)[19].

ADAM symptoms are divided in physical (decreased bone mineral density, decreased muscle mass and strength, increased body fat and body mass index, gynecomastia, anemia and fatigue), psychological (depressed mood, diminished energy, diminished sense of vitality or well-being, impaired cognition and memory) and sexual (diminished libido, ED, difficulty achieving orgasm, decreased morning erections, decreased performance)[20].

Testosterone replacement therapy (TRT) can improve many of the associated symptoms (mostly low libido, energy, mood, low muscle mass, osteoporosis and hot flushes). TRT is only indicated when the patient has symptoms and a corroborated low testosterone level[19].

In patients with PCa or at risk of PCa [first degree relatives with PCa, prostate specific antigen (PSA) > 4 ng/mL, palpable prostate nodules, PSA dynamics], treatment is controversial and assessment by an urologist is recommended[21]. Several studies have questioned the possible deleterious effects of TRT in patients with PCa. Recently, a meta-analysis showed no statistically significant differences in terms of progression or development of PCa, particularly with short term use (less than 12 mo)[22]. Also, in a study using the Surveillance, Epidemiology and End Results Program (SEER) database, Kaplan *et al*[23] showed that 0.79% of the patients who were diagnosed with PCa from 1992-2007 received TRT. In their analysis, they found a statistically significant higher overall and cancer specific mortality in patients not receiving TRT in comparison to those who did receive TRT. The need of salvage ADT was not different in both groups, reflecting similar cancer control.

Testosterone replacement in patients with diagnosis or high risk factors for PCa is still very controversial and no formal recommendations can be made in favor of such therapy.

OSTEOPOROSIS

After age 45, about 25% of male patients suffer some degree of osteoporosis. Risk factors are hypogonadism, alcohol abuse, smoking, sedentary lifestyle and calcium and vitamin D deficiency[7]. Osteopenia is defined as a T score between -1.5 and -2.4, and osteoporosis as a T score greater than -2.5, according to the World Health Organization[24]. It is recommended that all men over 50 years of age take calcium (1200 mg/d) and vitamin D supplements (800-1200 IU/d) along with exercise, quit smoking and limit alcohol drinking, regardless of ADT[25]. In men with prostate cancer, dose of supplementation has not been well established[26]. It is recommended that patients should be evaluated with a dual-energy X-ray absorptiometry (DXA) before initiation of ADT[27]. Further DXA should be done according to the results of the basal exam. Osteoporotic patients should have a DXA done every 6 mo, osteopenic patients every year and patients with a normal DXA can do the next exam up to 24 mo after the previous, provided they do not have high risk factors[28].

ADT has been proven to cause a decreased bone mineral density (BMD), independent of the modality used (either pharmacological or surgical blockade)[24]. During ADT, bone remodeling takes place, osteoclast activity seems to be increased whereas osteoblast repair is insufficient[29]. Such phenomenon causes decreased BMD and increases bone fracture risk and clinical fractures[30,31]. In a study by Shahinian *et al*[32] using the SEER database, the fracture rate for patients using gonadotropin releasing hormone (GNRH) agonists was 19.4% *vs* 12.6% in the non-ADT group. The risk was higher for patients receiving ≥ 9 doses of medication and orchiectomized[32]. The rate of decrease in BMD is 3%-5.6% during the first year of ADT and 1.1%-2.3% a year from the second year on[33]. The longer the time of ADT, the patients have a greater risk of having clinically significant fractures[34]. Also, in patients with osteoporosis the standardized mortality ratio after fractures increased according to the site of fracture (1.45 for minor fractures and 3.17 for proximal femur fractures)[35]. The use of calcium and vitamin D supplements is a possible treatment. Nevertheless, calcium supplementation has been associated with aggressive prostate tumors and increased cardiovascular disease[26].

It has been suggested that ADT should be avoided in patients with a high fracture-risk (age ≥ 80 years old, diabetes mellitus, alcoholism, cigarette smoking, rheumatoid disease, moderate-severe liver disease, paralysis and/or history of osteoporosis and fractures)[36]. The use of estrogens [diethylstilbestrol 1 mg/d orally (PO) or polyestradiol phosphate] for ADT may be the better option for high-risk patients. The cardiovascular effects of the latter medication have been minimized according to recent studies, and the repercussion on skeletal-related events seems less than using other ADT strategies[37].

Patients can be initially treated in a conservative fashion with smoking[38] cessation, controlled exercise, adequate calcium (1200 mg/d) and vitamin D (400-800 IU/d) intake as the first line of treatment. The initiation of exercise within 10 d from the first dose of ADT improves BMD compared to usual care. For more advanced cases the use of bisphosphonates is advised. The above mentioned therapies have shown benefits in prostate cancer patients receiving ADT[39], or even before initiation of ADT[27]. The use of alendronate (70 mg PO weekly) has showed benefits in patients with prostate cancer and osteoporosis or severe osteopenia[40,41]. For patients with non-metastatic disease, bisphosphonates can keep the BMD stable[42].

Denosumab, a human monoclonal antibody against the receptor of the nuclear factor-κβ ligand, has proven better in terms of risk of fracture and BMD increase on patients with ADT, compared to placebo[43,44]. Also, in a randomized study with 1904 patients with metastasis and castration resistant disease, denosumab 120 mg subcutaneously was compared against zoledronic acid 4 mg IV.

Denosumab was better for prevention of skeletal-events; adverse events were similar for both groups[45]. Both, denosumab and zolendronic acid can cause osteonecrosis of the jaw and hypocalcemia[45]. Bisphosphonates can cause nephrotoxicity, particularly in patients with chronic kidney failure and also a flu-like condition during the first doses[28].

Even though several studies have pointed to the benefits of exercise in different aspects of PCa and ADT related adverse effects, such strategy is still poorly applied. Osteoporosis and fracture prevention strategies are unknown to many patients and therefore underutilized[46].

OBESITY

Other side effects of ADT are a loss of lean muscle mass and a gain in body fat[47], particularly subcutaneous fat[48]. It causes a weight gain of about 1.8%-2.4% and an increase in fat body mass by 9.4%-11%[48,49]. The term used to describe the increased body fat along with decreased lean muscle mass that characterizes ADT-induced obesity is "Sarcopenic Obesity"[50]. Sarcopenia is reported in about 20% of patients with an average lean muscle mass loss of 2.8%[51].

Obesity and increased insulin secretion have been related to an increased incidence and more aggressive PCa[52,53]. Obese patients have increased progression to castration-resistant disease; increased rate of metastasis development and some authors have proposed a relationship between obesity and larger cancer specific mortality[54]. Obese patients have an increased oxidative stress, predisposing them to the development of several cancers such as endometrial, bladder, breast and prostate[55].

A structured exercise program, including both resistance and aerobic exercises helps against the metabolic complications of ADT. In a randomized trial by Cormie *et al*[38] the initiation of such exercise program at the beginning of ADT has improved outcomes in terms of lean muscle mass and less fat body mass. Such improvement is evident within the first 3 mo of treatment[38].

CARDIOVASCULAR COMPLICATIONS

These have been described in about 30% of patients undergoing ADT (intermittent and continuous). Also, cardiovascular death events happen in around 8% of such patients[10]. In a large study, comparing PCa patients without ADT with patients using GNRH agonists and surgically castrated patients, increased coronary heart disease (CHD), myocardial infarctions (MI) and sudden cardiac death (SCD) were seen in both ADT modalities[17]. Nevertheless, other large studies have not shown such findings in orchidectomized patients, only showing them in the group receiving GNRH agonists[56]. Estimated increased risk using ADT is 16% for CHD, 11% for MI and 16% for SCD[50]. In a comparative study of abiraterone *vs* placebo in patients with metastatic PCa, cardiovascular events occurred in 13% of patients in the abiraterone group *vs* 11% in the placebo group[57]. Recently, an observational study found that risk factors for developing cardiovascular diseases using ADT are the same than those for patients not receiving such therapy[58]. Screening strategies for cardiovascular disease should not change for patients whether or not they receive ADT.

In a comparative analysis of patients receiving GNRH agonists *vs* antagonists, interesting differences were found in terms of cardiovascular complications. There were no differences among men without preexisting cardiovascular disease. On the other hand, when analyzing patients with a previous history of cardiovascular disease, there was a 56% less chance of cardiovascular events or death within the first year of treatment in the GNRH antagonist group compared to the group receiving GNRH agonists (6.5% *vs* 14.7%)[59].

In a multicenter study by Galvão *et al*[60], they compared the benefit of 6 mo of supervised exercise training (resistance and aerobic training) followed by 6 mo of home training routines *vs* 12 mo of handouts of printed educational material of physical activity. Self-reported physical functioning, and objective measurements of muscle strength were better for the supervised group at 6 and 12 mo. Blood values showed little change between groups[60]. This should be taken into account when recommending exercise to patients; supervised training should be encouraged.

In conclusion, there is no definitive evidence about an increased cardiovascular death in patients using ADT, but they do seem to have more cardiovascular events. This is something physicians must keep in mind and make patients aware of when starting ADT. In selected patients with known cardiovascular disease, revascularization previous to starting ADT can improve survival[61].

METABOLIC SYNDROME

An increased incidence of metabolic syndrome (MetS) has been described, particularly in the group of PCa patients receiving ADT (50% *vs* 20% of naive patients)[62]. When patients with MetS are analyzed, they appear to have an increased risk for PCa (particularly clinically significant PCa, intermediate/high-risk tumors, progression and upgrading after surgery)[63-66]. The more elements of MetS they have, the greater the risk of PCa[67]. Specifically, high blood pressure and high body mass index are the two most relevant factors in terms of PCa death[68]. The possible explanations for this increased aggressiveness are the state of chronic inflammatory, high insulin levels, increased leptin and low adiponectin, and increased estrogen levels[63].

Saylor *et al*[50] recently reviewed the effect of ADT on the different MetS components. Patients showed a weight gain of 2% in the first year, 4%-8% fat body weight increase by the third month and 10% after 12 mo, lean muscle mass decrease of 3% by 12 mo, 26% increase in triglycerides by 6 mo, 8%-20% HDL increase by a year, 7% LDL increase by the third month, 26%-65% increase

in fasting plasma insulin and a 13% decrease in insulin sensitivity index. ADT confers a 44% risk of developing diabetes mellitus.

It is important to mention that unlike the "regular MetS", when patients receive ADT they gain mostly subcutaneous fat, not visceral fat; HDL increases instead of decreasing; blood pressure, waist-hip ratio and inflammatory markers such as C-reactive protein remain unchanged[49,69]. Also, patients on ADT do not develop non-alcoholic steatohepatitis[70]. These different features of the "ADT-related" MetS, perhaps, should be considered and treated independently as it is not a systemic inflammatory condition as opposed to the "regular MetS".

A supervised exercise program twice a week including aerobic and resistance training at the initiation of ADT offers benefits by reducing changes in body composition, physical function, lipid profile, sexual function and psychological distress[38]. The use of metformin along with an exercise program have shown improved outcomes in terms of blood pressure and body weight[62]. Metformin can control MetS, but also has an anti-proliferative effect by inhibiting the anabolic stimulation of insulin and activating the 5'-adenosine monophosphate-activation protein kinase[70].

Finally, the relation between MetS and PCa appears to be bidirectional. MetS could increase the risk of PCa, specifically aggressive and clinically significant tumors. On the other hand, patients with PCa and ADT have a high incidence of a "MetS-like" condition. Metformin, exercise, and other alternatives like statins and orlistat, can play an important role in treatment of patients with ADT and MetS.

INSULIN RESISTANCE AND LIPID ALTERATIONS

An increase in triglycerides and cholesterol levels is seen after ADT[49]. These side effects are more significant within the first 12 wk of therapy[71].

The incidence of diabetes mellitus increases with both, pharmacological and surgical ADT[17]. In only 12 wk, glycosylated hemoglobin and fasting plasma insulin levels increase significantly. By the same time, insulin sensitivity decreases[71]. There is an increase in glycosylated hemoglobin (HbA1c) of 0.13% after two years of treatment in non-previously diabetic patients[42].

It has been proposed, that the insulin increase in patients after ADT causes an increase in insulin-like growth factor (IGF-1). While this last situation could control the metabolic effects of ADT, it might also favor the development of castrate-resistant prostate cancer (CRPC). The insulin increase appears to stimulate intra-tumoral androgen synthesis, leading to CRPC development[72]. It seems that IGF-1 proteins can be involved in the change from benign cells to malignant prostate cancer cells. This is a hypothesis that explains why diabetics, obese individuals and patients with insulin resistance develop more PCa and more aggressive variants of PCa. Specifically, these patients have a shorter time between biochemical recurrence to the development of CRPC. Perhaps, diabetes treatment in patients with ADT is beneficial not only against the hyperglycemic state, but also to control IGF-1 and progression to CRPC[73].

Interestingly, some diabetic and weight control medication such as metformin, orlistat, statins and thiazolidinediones, could control cancer progression promoting apoptosis, decreasing cell mitosis and increasing sensitivity to chemotherapeutic agents[55]. Among these, metformin is the most studied medication; with a good safety profile it improves the lipid results, normalizes insulin levels and does not cause dysglycemia in non-diabetic patients.

As ADT increases insulin and causes insulin resistance, the development of diabetes is not the only complication we should worry about. The relationship between insulin rises and disease progression to CRPC is something we should be aware of. Perhaps, metformin should become an imperative companion to ADT. We recommend performing a metabolic assessment including fasting plasma glucose, HbA1c and a lipid profile every six months during the first year of initiating ADT, followed by yearly assessment thereafter; even in patients on intermittent ADT.

FRAILTY SYNDROME

With the growing age of the population and the survival rate of patients with PCa, disability has become a growing issue that should be taken into consideration by the treating physician. Disability, referred to as the dependency of another person to perform ADL, can happen due to several causes including weakness, comorbidities and aging[4]. Similarly, inflammatory markers such as IGF-1 (which is frequently elevated during ADT), predispose patients to the development of frailty syndrome[74,75].

In a large prospective cohort, Rockwood *et al*[76] developed a scale known as "Frailty Index". After a 5-year follow-up, such scale correlated with the risk of death and the risk of entry to an institution. This is a simple tool that can be applied to patients with PCa. In general, Frailty Syndrome (FS) is characterized by the presence of $\geqslant$ 3 of the following conditions: weight loss, weakness, fatigue, low activity and slow motion performance with balance and gait abnormalities[77,78]. Also, a "Pre-Frailty" condition has been described in which patients can either develop a full-blown FS or recover[4,77]. Early detection is a major intervention for such patients. Pre-Frailty patients must be advised of the increased risk of a worsening condition.

ADT can cause FS. Sarcopenia in patients with ADT can have the same impact as weight loss[77]. The "weight loss" definition for FS is recognized as an unintentional loss of > 10 pounds (4.5 kg) in the last year. Furthermore, obesity is recognized as a risk factor for the development of FS[79]. Weakness is defined as low grip strength measured with a hand-held dynamometer. Weakness can also

be caused by ADT[80]. A 15 feet (4.6 m) walk (speed less than 0.8-1 m/s) evaluates motion performance, which can be affected by a hypogonadal state[74,81]. Fatigue, is a well known side effect of ADT that will be discussed later in this review. Low physical activity can be caused by sarcopenia as well. Finally, as most patients with PCa are older than 65 years old, this is also a contributing factor for the development of FS[82].

FS has been associated with increased mortality, hospitalizations and worsening daily functions. Risk of falls and dependency are also increased in patients receiving ADT[77,83].

We advise physicians to perform scrutiny of FS before starting ADT. Patients with Pre-Frailty should be recognized and conditions optimized (weight loss, exercise routine, dietary advice) before ADT initiation.

LOSS OF LIBIDO AND ERECTILE DYSFUNCTION

Loss of libido is quite frequent in patients with ADT. Within the first year of ADT, 80% of patients without previous erectile dysfunction refer to having impotence[84]. The reason is a lack of testosterone stimuli. Patients often stop having sexual impulse and difficulty achieving an erection good enough for sexual intercourse. This leads to and avoidance of sexual contact because they might feel ashamed. Evaluation consists on interrogation of the patient and partner. Questionnaires such as the International Index of Erectile Function can be used to standardize results.

First line of treatment is the use of phosphodiesterase inhibitors, although the benefit is not always as good as with patients without ADT. Contraindications such as severe coronary artery disease, severe liver failure, nitrate therapy, *etc*. should be considered before initiation of therapy. Other options are penile prosthesis, vacuum devices and intracavernosal injections of prostaglandins[28].

FATIGUE

Fatigue in prostate cancer may be related to the loss of lean muscle mass, gain of body fat, and/or emotional distress in patients undergoing ADT[85,86]. Fatigue is described in about 40% of these patients[87]. With the use of enzalutamide fatigue was reported in 34% of patients (*vs* 29% in the placebo group)[88], and with abiraterone 44% (*vs* 43% in the placebo group)[57].

Cancer-related fatigue can be improved by aerobic exercise[89]. Better outcomes have been shown in group-exercise programs and in such programs including resistance training. Exercise should be recommended under supervision whenever it is possible[90,91]. Increased muscle mass and muscle strength can be obtained along with improved quality of life and fatigue[91,92].

In conclusion, supervised resistance and aerobic exercise is recommended two to three times a day in order to improve muscle mass, strength and fatigue.

COGNITIVE DECLINE

Even though there is not much evidence regarding cognitive decline associated with ADT, both transdermal estrogen therapy and exercise programs can improve this possible side effect[87]. Cognitive decline happens in up to 48% of patients on ADT[93]. Most studies assessing cognitive affection include a small number of patients. The most affected areas of cognition are executive, verbal and spatial functioning[28]. Mini-Mental Exam can be used as a standardized evaluation.

The reason for the mental decline during ADT might be an affection of the sex-steroid receptors in prefrontal cortex and hypothalamus. Gonadectomy in animals causes a decrease in 40% of synaptic unions that can be restored by androgen replacement. Transdermal estradiol (0.6 mg/24 h) applied every 7 d can improve memory loss[94].

Because of the safety profile, the most recommended strategy is a resistance and aerobic exercise program. Mental health and psychological distress benefits are evident after 3 mo of supervised exercise[38].

In a study including patients receiving ADT for causes other than PCa, ADT receiving patients had better scores of "agreeableness" (kind, cooperative and considerate personality) compared to patients not on ADT. This was the only significantly affected element of the "Big Five Personality Traits"[95].

Depression diagnosis can be made in a quarter of patients. Nevertheless, such diagnosis cannot be completely attributed to ADT[51]. According to a SEER study, ADT by itself does not increase the possibilities of developing depression[96]. Either way, PCa patients have a raised incidence of depression (seems to be multifactorial). Periodic evaluation of depressive symptoms and psychiatric attention to those with positive results should be part of the multidisciplinary approach. Interrogation of the patient's partner can be useful for gathering information.

VASOMOTOR FLUSHING

This is the most frequently found side effect of ADT (about 75% of patients with ADT). Interestingly, with the use of enzalutamide the reported incidence is much lower (20%)[88]. It is referred to as sweating, flushing of the upper body and a feeling of anxiety that lasts for about 3-10 min. Mean time of appearance is 2.7 mo after the start of ADT[97]. The physiopathologic explanation for such phenomenon seems to be an affection of the hypothalamic thermoregulatory center due to sex hormones, affecting serotonin and norepinephrine amounts at this level[98]. The psychological affection in these patients is quite relevant, feeling an impact in masculinity, powerlessness against such symptoms and social embarrassment[99]. A classification of the severity of hot flashes is used frequently[100].

Behavioral modifications oriented to keeping a low body temperature (dressing with cool cloth, drinking cold beverages, using a fan, avoiding spicy food, *etc*.) are

the first line of therapy when facing a patient with hot flushes[101,102].

Several strategies have been attempted in order to improve hot flushes. Estrogen and progesterone supplements are effective in about 85%-91% of patients (medroxyprogesterone acetate 5 mg twice daily[11] PO or 400 mg intramuscular, and megestrol acetate 20-40 mg bid PO)[97,103]. This seems to be the most effective therapy[98]. One should be aware of case-reports about a decrease in PSA levels when megestrol acetate is discontinued, considering it a possible tumor growth-stimulant when patients' PSA levels increase under such treatment. This last phenomenon may require suspension of megestrol acetate[104].

One-milligram diethylstilbestrol has shown effectiveness in 70% of patients, with no increase in thromboembolic or cardiovascular complications. There is concern about the increased risk of breast cancer in women, although it has not been well studied in men with ADT.

Gabapentin has been used in both men and women experiencing hot flushes. In men, it has an efficacy of up to 49% with a 300-900 mg/d dose. Side effects include nausea, loss of appetite, vomiting, dizziness and somnolence[105,106].

Anti-depressive medications such as Venlafaxine (serotonin and norepinephrine reuptake inhibitor) and paroxetine have achieved symptomatic reduction (about 55% with Venlafaxine) with few side effects (dry mouth, weight gain, nausea, headache and decreased appetite[87]) and improvement in fatigue, diaphoresis and sleeping trouble[107]. Unfortunately, these are mostly from small trials as well as evidence derived from menopausal women[108]. Caution should be exercised when using abiraterone acetate since this medication could narrow therapeutic index[104].

A large randomized trial, including 919 patients comparing vanlafaxine 75 mg/d, cyproterone acetate and medroxyprogesterone acetate 20 mg/d proved a significant benefit from all therapies (-47.2%, -94.5% and -83.7% after 4 wk, and -56.7%, -100% and -97.3% after 8 wk from randomization, respectively). No statistically significant difference was found in cyproterone and medroxyprogesterone groups[109].

Some medications such as vitamin E and Clonidine have been used in women, although benefit has not been proven in men and they have significant side effects, therefore are not recommended. Acupuncture electrostimulated and traditional[110], has also been studied in small trials. One systematic review assessed the utility of acupuncture in patients with PCa and was unable to recommend such therapy[111].

With such high incidence, vasomotor flushing risk should be commented with the patients and behavioral recommendations should be given to every patient from the beginning. If conservative treatment is not enough, the other available strategies can be considered according to the benefits and specific side effects.

OTHER COMPLICATIONS

Other complications such as gynecomastia can develop with ADT, interfering with patients social performance in up to 28% of cases[51]. Penile length decrease of > 1 cm was reported by 93% of patients in one study[112]. A hemoglobin decline of -1.11 g/dL (normocytic normochromic) has been reported, and most patients are asymptomatic[113]. We recommend an assessment prior to initiation of ADT and a complete evaluation if positive for anemia. Further testing every 3-6 mo should be done depending on hemoglobin values.

CONCLUSION

Prostate cancer and ADT is nowadays a common combination. ADT represents one of the most utilized therapies for PCa and can be implemented in nearly every stage of the disease. Side effects are frequent and can have serious implications in quality of life or even mortality. All types of ADT are prone to present side effects, with certain differences among the different modalities. Adherence to guidelines has great implications on patients. Individual patient selection, surveillance of complications and educational strategies (for both patient and urologists) are important cues in treatment.

REFERENCES

1 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]

2 **D'Amico AV**, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Beard CJ, Wein A. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; **280**: 969-974 [PMID: 9749478]

3 **Nguyen-Nielsen M**, Nørgaard M, Jacobsen JB, Borre M, Thomsen RW, Søgaard M. Comorbidity and survival of Danish prostate cancer patients from 2000-2011: a population-based cohort study. *Clin Epidemiol* 2013; **5**: 47-55 [PMID: 24227923]

4 **Topinková E**. Aging, disability and frailty. *Ann Nutr Metab* 2008; **52** Suppl 1: 6-11 [PMID: 18382070]

5 **Huggins C**, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J Clin* 1972; **22**: 232-240 [PMID: 4625049]

6 **Dorff TB**, Glode LM. Current role of neoadjuvant and adjuvant systemic therapy for high-risk localized prostate cancer. *Curr Opin Urol* 2013; **23**: 366-371 [PMID: 23619581 DOI: 10.1097/MOU.0b013e328361d467]

7 **Isbarn H**, Boccon-Gibod L, Carroll PR, Montorsi F, Schulman C, Smith MR, Sternberg CN, Studer UE. Androgen deprivation therapy for the treatment of prostate cancer: consider both benefits and risks. *Eur Urol* 2009; **55**: 62-75 [PMID: 18945543 DOI: 10.1016/j.eururo.2008.10.008]

8 **Makarov DV**, Humphreys EB, Mangold LA, Carducci MA, Partin AW, Eisenberger MA, Walsh PC, Trock BJ. The natural history of men treated with deferred androgen deprivation therapy in whom metastatic prostate cancer developed following radical prostatectomy. *J Urol* 2008; **179**: 156-161; discussion 161-162 [PMID: 18001801 DOI: 10.1016/j.juro.2007.08.133]

9 **Bourke L**, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW, Saxton JM, Rosario DJ. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. *Eur Urol* 2014; **65**: 865-872 [PMID: 24119318 DOI: 10.1016/j.eururo.2013.09.040]

10 **Salonen AJ**, Taari K, Ala-Opas M, Viitanen J, Lundstedt S, Tammela TL. Advanced prostate cancer treated with intermittent or continuous androgen deprivation in the randomised FinnProstate Study VII: quality of life and adverse effects. *Eur Urol* 2013; **63**: 111-120 [PMID: 22857983 DOI: 10.1016/j.eururo.2012.07.040]

11 **Crook JM**, O'Callaghan CJ, Duncan G, Dearnaley DP, Higano CS, Horwitz EM, Frymire E, Malone S, Chin J, Nabid A, Warde P, Corbett T, Angyalfi S, Goldenberg SL, Gospodarowicz MK, Saad F, Logue JP, Hall E, Schellhammer PF, Ding K, Klotz L. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012; **367**: 895-903 [PMID: 22931259 DOI: 10.1056/NEJMoa1201546]

12 **Botrel TE**, Clark O, dos Reis RB, Pompeo AC, Ferreira U, Sadi MV, Bretas FF. Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. *BMC Urol* 2014; **14**: 9 [PMID: 24460605 DOI: 10.1186/1471-2490-14-9]

13 **Conti PD**, Atallah AN, Arruda H, Soares BG, El Dib RP, Wilt TJ. Intermittent versus continuous androgen suppression for prostatic cancer. *Cochrane Database Syst Rev* 2007; (**4**): CD005009 [PMID: 17943832 DOI: 10.1002/14651858.CD005009.pub2]

14 **Gandaglia G**, Sun M, Hu JC, Novara G, Choueiri TK, Nguyen PL, Schiffmann J, Graefen M, Shariat SF, Abdollah F, Briganti A, Montorsi F, Trinh QD, Karakiewicz PI. Gonadotropin-releasing Hormone Agonists and Acute Kidney Injury in Patients with Prostate Cancer. *Eur Urol* 2014; Epub ahead of print [PMID: 24495466 DOI: 10.1016/j.eururo.2014.01.026]

15 **Hussain M**, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Kanaga Sundaram S, Small EJ, Dawson NA, Donnelly BJ, Venner PM, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Ely B, Moinpour CM, Vogelzang NJ, Thompson IM. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med* 2013; **368**: 1314-1325 [PMID: 23550669 DOI: 10.1056/NEJMoa1212299]

16 **Higano CS**. Intermittent versus continuous androgen deprivation therapy. *J Natl Compr Canc Netw* 2014; **12**: 727-733 [PMID: 24812139]

17 **Keating NL**, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006; **24**: 4448-4456 [PMID: 16983113 DOI: 10.1200/JCO.2006.06.2497]

18 **Feldman HA**, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab* 2002; **87**: 589-598 [PMID: 11836290 DOI: 10.1210/jcem.87.2.8201]

19 **McGill JJ**, Shoskes DA, Sabanegh ES. Androgen deficiency in older men: indications, advantages, and pitfalls of testosterone replacement therapy. *Cleve Clin J Med* 2012; **79**: 797-806 [PMID: 23125330 DOI: 10.3949/ccjm.79a.12010]

20 **Traish AM**, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. *Am J Med* 2011; **124**: 578-587 [PMID: 21683825 DOI: 10.1016/j.amjmed.2010.12.027]

21 **Bhasin S**, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; **95**: 2536-2559 [PMID: 20525905 DOI: 10.1210/jc.2009-2354]

22 **Cui Y**, Zong H, Yan H, Zhang Y. The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2014; **17**: 132-143 [PMID: 24445948 DOI: 10.1038/pcan.2013.60]

23 **Kaplan AL**, Trinh QD, Sun M, Carter SC, Nguyen PL, Shih YC, Marks LS, Hu JC. Testosterone replacement therapy following the diagnosis of prostate cancer: outcomes and utilization trends. *J Sex Med* 2014; **11**: 1063-1070 [PMID: 24443943 DOI: 10.1111/jsm.12429]

24 **Morote J**, Martinez E, Trilla E, Esquena S, Abascal JM, Encabo G, Reventós J. Osteoporosis during continuous androgen deprivation: influence of the modality and length of treatment. *Eur Urol* 2003; **44**: 661-665 [PMID: 14644117]

25 **Planas Morin J**, Celma Domenech A, Placer Santos J, Trilla Herrera E, Salvador Lacambra C, Lorente Garcia D, Regis L, Carles Galceran J, Morote Robles J. Bone mass behavior after 1 year of different treatment strategies in prostate cancer patients subjected to androgen deprivation therapy. *Rheumatol Int* 2014; **34**: 1419-1425 [PMID: 24615021 DOI: 10.1007/s00296-014-2977-3]

26 **Datta M**, Schwartz GG. Calcium and vitamin D supplementation during androgen deprivation therapy for prostate cancer: a critical review. *Oncologist* 2012; **17**: 1171-1179 [PMID: 22836449 DOI: 10.1634/theoncologist.2012-0051]

27 **Lassemillante AC**, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. *Endocrine* 2014; **45**: 370-381 [PMID: 24174178 DOI: 10.1007/s12020-013-0083-z]

28 **Mohile SG**, Mustian K, Bylow K, Hall W, Dale W. Management of complications of androgen deprivation therapy in the older man. *Crit Rev Oncol Hematol* 2009; **70**: 235-255 [PMID: 18952456 DOI: 10.1016/j.critrevonc.2008.09.004]

29 **Theresa A**, Guise JAE. Cancer Treatment-Induced Bone Loss (CTIBL) in Prostate Cancer- Pathophysiology, Preclinical Findings, and Treatment with Zolendronic Acid. *Eur Urol* 2004; (**3**) Suppl: 46-54 [DOI: 10.1016/j.eursup.2004.08.012]

30 **Melton LJ**, Alothman KI, Khosla S, Achenbach SJ, Oberg AL, Zincke H. Fracture risk following bilateral orchiectomy. *J Urol* 2003; **169**: 1747-1750 [PMID: 12686824 DOI: 10.1097/01.ju.0000059281.67667.97]

31 **Smith MR**, Boyce SP, Moyneur E, Duh MS, Raut MK, Brandman J. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol* 2006; **175**: 136-139; discussion 139 [PMID: 16406890 DOI: 10.1016/S0022-5347(05)00033-9]

32 **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 [PMID: 15647578 DOI: 10.1056/NEJMoa041943]

33 **Rizzoli R**, Body JJ, Brandi ML, Cannata-Andia J, Chappard D, El Maghraoui A, Glüer CC, Kendler D, Napoli N, Papaioannou A, Pierroz DD, Rahme M, Van Poznak CH, de Villiers TJ, El Hajj Fuleihan G. Cancer-associated bone disease. *Osteoporos Int* 2013; **24**: 2929-2953 [PMID: 24146095 DOI: 10.1007/s00198-013-2530-3]

34 **Smith MR**, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol* 2005; **23**: 7897-7903 [PMID: 16258089 DOI: 10.1200/JCO.2004.00.6908]

35 **Center JR**, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 1999; **353**: 878-882 [PMID: 10093980 DOI: 10.1016/S0140-6736(98)09075-8]

36 **Shao YH**, Moore DF, Shih W, Lin Y, Jang TL, Lu-Yao GL. Fracture after androgen deprivation therapy among men with a high baseline risk of skeletal complications. *BJU Int* 2013; **111**: 745-752 [PMID: 23331464 DOI: 10.1111/j.1464-410X.2012.11758.x]

37 **Oefelein MG**, Resnick MI. The impact of osteoporosis in men treated for prostate cancer. *Urol Clin North Am* 2004; **31**:

313-319 [PMID: 15123410 DOI: 10.1016/j.ucl.2004.02.002]
38 **Cormie P**, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, Chambers SK, Newton RU. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU Int* 2014; Epub ahead of print [PMID: 24467669 DOI: 10.1111/bju.12646]
39 **Zhumkhawala AA**, Gleason JM, Cheetham TC, Niu F, Loo RK, Dell RM, Jacobsen SJ, Chien GW. Osteoporosis management program decreases incidence of hip fracture in patients with prostate cancer receiving androgen deprivation therapy. *Urology* 2013; **81**: 1010-1015 [PMID: 23490521 DOI: 10.1016/j.urology.2012.11.066]
40 **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 [PMID: 23040208 DOI: 10.1016/j.eururo.2012.09.007]
41 **Planas J**, Trilla E, Raventós C, Cecchini L, Orsola A, Salvador C, Placer J, Encabo G, Morote J. Alendronate decreases the fracture risk in patients with prostate cancer on androgen-deprivation therapy and with severe osteopenia or osteoporosis. *BJU Int* 2009; **104**: 1637-1640 [PMID: 19549260 DOI: 10.1111/j.1464-410X.2009.08622.x]
42 **Cheung AS**, Pattison D, Bretherton I, Hoermann R, Lim Joon D, Ho E, Jenkins T, Hamilton EJ, Bate K, Chan I, Zajac JD, Grossmann M. 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 [PMID: 23686896 DOI: 10.1111/j.2047-2927.2013.00093.x]
43 **Egerdie RB**, Saad F, Smith MR, Tammela TL, Heracek J, Sieber P, Ke C, Leder B, Dansey R, Goessl C. Responder analysis of the effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. *Prostate Cancer Prostatic Dis* 2012; **15**: 308-312 [PMID: 22641239 DOI: 10.1038/pcan.2012.18]
44 **Smith MR**, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, Heracek J, Szwedowski M, Ke C, Kupic A, Leder BZ, Goessl C. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009; **361**: 745-755 [PMID: 19671656 DOI: 10.1056/NEJMoa0809003]
45 **Fizazi K**, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011; **377**: 813-822 [PMID: 21353695 DOI: 10.1016/S0140-6736(10)62344-6]
46 **Nadler M**, Alibhai S, Catton P, Catton C, To MJ, Jones JM. Osteoporosis knowledge, health beliefs, and healthy bone behaviours in patients on androgen-deprivation therapy (ADT) for prostate cancer. *BJU Int* 2013; **111**: 1301-1309 [PMID: 23351062 DOI: 10.1111/j.1464-410X.2012.11777.x]
47 **van Londen GJ**, Levy ME, Perera S, Nelson JB, Greenspan SL. Body composition changes during androgen deprivation therapy for prostate cancer: a 2-year prospective study. *Crit Rev Oncol Hematol* 2008; **68**: 172-177 [PMID: 18706829 DOI: 10.1016/j.critrevonc.2008.06.006]
48 **Smith MR**. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology* 2004; **63**: 742-745 [PMID: 15072892 DOI: 10.1016/j.urology.2003.10.063]
49 **Smith MR**, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, Kantoff PW. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab* 2002; **87**: 599-603 [PMID: 11836291 DOI: 10.1210/jcem.87.2.8299]
50 **Saylor PJ**, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol* 2013; **189**: S34-42; discussion S43-S44 [PMID: 23234628 DOI: 10.1016/j.juro.2012.11.017]
51 **Walker LM**, Tran S, Robinson JW. Luteinizing hormone--releasing hormone agonists: a quick reference for prevalence rates of potential adverse effects. *Clin Genitourin Cancer* 2013; **11**: 375-384 [PMID: 23891497 DOI: 10.1016/j.clgc.2013.05.004]
52 **Grossmann M**, Zajac JD. Hematological changes during androgen deprivation therapy. *Asian J Androl* 2012; **14**: 187-192 [PMID: 22231300 DOI: 10.1038/aja.2011.102]
53 **MacInnis RJ**, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. *Cancer Causes Control* 2006; **17**: 989-1003 [PMID: 16933050 DOI: 10.1007/s10552-006-0049-z]
54 **Keto CJ**, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, Freedland SJ. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. *BJU Int* 2012; **110**: 492-498 [PMID: 22094083 DOI: 10.1111/j.1464-410X.2011.10754.x]
55 **Gunter JH**, Sarkar PL, Lubik AA, Nelson CC. New players for advanced prostate cancer and the rationalisation of insulin-sensitising medication. *Int J Cell Biol* 2013; **2013**: 834684 [PMID: 23573093 DOI: 10.1155/2013/834684]
56 **Jespersen CG**, Nørgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. *Eur Urol* 2014; **65**: 704-709 [PMID: 23433805 DOI: 10.1016/j.eururo.2013.02.002]
57 **de Bono JS**, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; **364**: 1995-2005 [PMID: 21612468 DOI: 10.1056/NEJMoa1014618]
58 **Keating NL**, O'Malley AJ, Freedland SJ, Smith MR. Does comorbidity influence the risk of myocardial infarction or diabetes during androgen-deprivation therapy for prostate cancer? *Eur Urol* 2013; **64**: 159-166 [PMID: 22537796 DOI: 10.1016/j.eururo.2012.04.035]
59 **Albertsen PC**, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol* 2014; **65**: 565-573 [PMID: 24210090 DOI: 10.1016/j.eururo.2013.10.032]
60 **Galvão DA**, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, Lamb DS, Chambers SK, Newton RU. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol* 2014; **65**: 856-864 [PMID: 24113319 DOI: 10.1016/j.eururo.2013.09.041]
61 **Nguyen PL**, Chen MH, Goldhaber SZ, Martin NE, Beard CJ, Dosoretz DE, Katin MJ, Ross R, Salenius SA, D'Amico AV. Coronary revascularization and mortality in men with congestive heart failure or prior myocardial infarction who receive androgen deprivation. *Cancer* 2011; **117**: 406-413 [PMID: 21108457 DOI: 10.1002/cncr.25597]
62 **Nobes JP**, Langley SE, Klopper T, Russell-Jones D, Laing RW. A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. *BJU Int* 2012; **109**: 1495-1502 [PMID: 21933330 DOI: 10.1111/j.1464-410X.2011.10555.x]
63 **De Nunzio C**, Aronson W, Freedland SJ, Giovannucci E,

Parsons JK. The correlation between metabolic syndrome and prostatic diseases. *Eur Urol* 2012; **61**: 560-570 [PMID: 22119157 DOI: 10.1016/j.eururo.2011.11.013]
64 **Kheterpal E**, Sammon JD, Diaz M, Bhandari A, Trinh QD, Pokala N, Sharma P, Menon M, Agarwal PK. Effect of metabolic syndrome on pathologic features of prostate cancer. *Urol Oncol* 2013; **31**: 1054-1059 [PMID: 23020926 DOI: 10.1016/j.urolonc.2011.12.012]
65 **Morote J**, Ropero J, Planas J, Bastarós JM, Delgado G, Placer J, Celma A, de Torres IM, Carles J, Reventós J, Doll A. Metabolic syndrome increases the risk of aggressive prostate cancer detection. *BJU Int* 2013; **111**: 1031-1036 [PMID: 22883053 DOI: 10.1111/j.1464-410X.2012.11406.x]
66 **Xiang YZ**, Xiong H, Cui ZL, Jiang SB, Xia QH, Zhao Y, Li GB, Jin XB. The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence. *J Exp Clin Cancer Res* 2013; **32**: 9 [PMID: 23406686 DOI: 10.1186/1756-9966-32-9]
67 **Bhindi B**, Locke J, Alibhai SM, Kulkarni GS, Margel DS, Hamilton RJ, Finelli A, Trachtenberg J, Zlotta AR, Toi A, Hersey KM, Evans A, van der Kwast TH, Fleshner NE. Dissecting the Association Between Metabolic Syndrome and Prostate Cancer Risk: Analysis of a Large Clinical Cohort. *Eur Urol* 2014; Epub ahead of print [PMID: 24568896 DOI: 10.1016/j.eururo.2014.01.040]
68 **Häggström C**, Stocks T, Ulmert D, Bjørge T, Ulmer H, Hallmans G, Manjer J, Engeland A, Nagel G, Almqvist M, Selmer R, Concin H, Tretli S, Jonsson H, Stattin P. Prospective study on metabolic factors and risk of prostate cancer. *Cancer* 2012; **118**: 6199-6206 [PMID: 23090855 DOI: 10.1002/cncr.27677]
69 **Smith MR**, Lee H, McGovern F, Fallon MA, Goode M, Zietman AL, Finkelstein JS. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. *Cancer* 2008; **112**: 2188-2194 [PMID: 18348297 DOI: 10.1002/cncr.23440]
70 **Conteduca V**, Di Lorenzo G, Bozza G, Ardito R, Aieta M. Metabolic syndrome as a peculiar target for management of prostate cancer patients. *Clin Genitourin Cancer* 2013; **11**: 211-220 [PMID: 23701880 DOI: 10.1016/j.clgc.2013.04.009]
71 **Smith MR**, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 2006; **91**: 1305-1308 [PMID: 16434464 DOI: 10.1210/jc.2005-2507]
72 **Lubik AA**, Gunter JH, Hendy SC, Locke JA, Adomat HH, Thompson V, Herington A, Gleave ME, Pollak M, Nelson CC. Insulin increases de novo steroidogenesis in prostate cancer cells. *Cancer Res* 2011; **71**: 5754-5764 [PMID: 21747118 DOI: 10.1158/0008-5472.CAN-10-2470]
73 **Aggarwal RR**, Ryan CJ, Chan JM. Insulin-like growth factor pathway: a link between androgen deprivation therapy (ADT), insulin resistance, and disease progression in patients with prostate cancer? *Urol Oncol* 2013; **31**: 522-530 [PMID: 21658978 DOI: 10.1016/j.urolonc.2011.05.001]
74 **Joseph C**, Kenny AM, Taxel P, Lorenzo JA, Duque G, Kuchel GA. Role of endocrine-immune dysregulation in osteoporosis, sarcopenia, frailty and fracture risk. *Mol Aspects Med* 2005; **26**: 181-201 [PMID: 15811434 DOI: 10.1016/j.mam.2005.01.004]
75 **Puts MT**, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol* (Oxf) 2005; **63**: 403-411 [PMID: 16181232 DOI: 10.1111/j.1365-2265.2005.02355.x]
76 **Rockwood K**, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; **173**: 489-495 [PMID: 16129869 DOI: 10.1503/cmaj.050051]
77 **Bylow K**, Mohile SG, Stadler WM, Dale W. Does androgen-deprivation therapy accelerate the development of frailty in older men with prostate cancer?: a conceptual review. *Cancer* 2007; **110**: 2604-2613 [PMID: 17960609 DOI: 10.1002/cncr.23084]
78 **Fried LP**, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; **59**: 255-263 [PMID: 15031310]
79 **Blaum CS**, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *J Am Geriatr Soc* 2005; **53**: 927-934 [PMID: 15935013 DOI: 10.1111/j.1532-5415.2005.53300.x]
80 **Basaria S**, Lieb J, Tang AM, DeWeese T, Carducci M, Eisenberger M, Dobs AS. Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clin Endocrinol* (Oxf) 2002; **56**: 779-786 [PMID: 12072048]
81 **Abellan van Kan G**, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. *Clin Geriatr Med* 2010; **26**: 275-286 [PMID: 20497846 DOI: 10.1016/j.cger.2010.02.002]
82 **Rockwood K**, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 2011; **27**: 17-26 [PMID: 21093719 DOI: 10.1016/j.cger.2010.08.008]
83 **Bylow K**, Dale W, Mustian K, Stadler WM, Rodin M, Hall W, Lachs M, Mohile SG. Falls and physical performance deficits in older patients with prostate cancer undergoing androgen deprivation therapy. *Urology* 2008; **72**: 422-427 [PMID: 18561991 DOI: 10.1016/j.urology.2008.03.032]
84 **Potosky AL**, Reeve BB, Clegg LX, Hoffman RM, Stephenson RA, Albertsen PC, Gilliland FD, Stanford JL. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. *J Natl Cancer Inst* 2002; **94**: 430-437 [PMID: 11904315]
85 **Boxer RS**, Kenny AM, Dowsett R, Taxel P. The effect of 6 months of androgen deprivation therapy on muscle and fat mass in older men with localized prostate cancer. *Aging Male* 2005; **8**: 207-212 [PMID: 16390748 DOI: 10.1080/13685530500361226]
86 **Galvão DA**, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, Rowling C, Prince R. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int* 2008; **102**: 44-47 [PMID: 18336606 DOI: 10.1111/j.1464-410X.2008.07539.x]
87 **Ahmadi H**, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. *BJU Int* 2013; **111**: 543-548 [PMID: 23351025 DOI: 10.1111/j.1464-410X.2012.11774.x]
88 **Scher HI**, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; **367**: 1187-1197 [PMID: 22894553 DOI: 10.1056/NEJMoa1207506]
89 **Cramp F**, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2012; **11**: CD006145 [PMID: 23152233 DOI: 10.1002/14651858.CD006145.pub3]
90 **Galvão DA**, Taaffe DR, Spry N, Newton RU. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer Prostatic Dis* 2007; **10**: 340-346 [PMID: 17486110 DOI: 10.1038/sj.pcan.4500975]
91 **Keogh JW**, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. *J Pain Symptom Manage* 2012; **43**: 96-110 [PMID: 21640547 DOI: 10.1016/j.jpainsymman.2011.03.006]
92 **Galvão DA**, Taaffe DR, Spry N, Joseph D, Newton RU.

Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol* 2010; **28**: 340-347 [PMID: 19949016 DOI: 10.1200/JCO.2009.23.2488]

93 **Green HJ**, Pakenham KI, Headley BC, Yaxley J, Nicol DL, Mactaggart PN, Swanson C, Watson RB, Gardiner RA. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. *BJU Int* 2002; **90**: 427-432 [PMID: 12175403]

94 **Beer TM**, Bland LB, Bussiere JR, Neiss MB, Wersinger EM, Garzotto M, Ryan CW, Janowsky JS. Testosterone loss and estradiol administration modify memory in men. *J Urol* 2006; **175**: 130-135 [PMID: 16406889 DOI: 10.1016/S0022-5347(05)00049-2]

95 **Treleaven MJR**, Roberts L, Wassersug RJ, Johnson T. Castration and Personality: Correlation of Androgen Deprivation and Estrogen Supplementation with the Big Five Factor Personality Traits of Adult Males. *J Res Pers* 2013; **47**: 376-379 [DOI: 10.1016/j.jrp.2013.03.005]

96 **Shahinian VB**, Kuo YF, Freeman JL, Goodwin JS. Risk of the "androgen deprivation syndrome" in men receiving androgen deprivation for prostate cancer. *Arch Intern Med* 2006; **166**: 465-471 [PMID: 16505268 DOI: 10.1001/archinte.166.4.465]

97 **Charig CR**, Rundle JS. Flushing. Long-term side effect of orchiectomy in treatment of prostatic carcinoma. *Urology* 1989; **33**: 175-178 [PMID: 2465644]

98 **Morrow PK**, Mattair DN, Hortobagyi GN. Hot flashes: a review of pathophysiology and treatment modalities. *Oncologist* 2011; **16**: 1658-1664 [PMID: 22042786 DOI: 10.1634/theoncologist.2011-0174]

99 **Eziefula CU**, Grunfeld EA, Hunter MS. ‚You know I've joined your club… I'm the hot flush boy': a qualitative exploration of hot flushes and night sweats in men undergoing androgen deprivation therapy for prostate cancer. *Psychooncology* 2013; **22**: 2823-2830 [PMID: 23893467 DOI: 10.1002/pon.3355]

100 **Langenstroer P**, Kramer B, Cutting B, Amling C, Poultan T, Lance R, Thrasher JB. Parenteral medroxyprogesterone for the management of luteinizing hormone releasing hormone induced hot flashes in men with advanced prostate cancer. *J Urol* 2005; **174**: 642-645 [PMID: 16006929 DOI: 10.1097/01.ju.0000165570.28635.4b]

101 **North American Menopause Society**. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004; **11**: 11-33 [PMID: 14716179 DOI: 10.1097/01.GME.0000108177.85442.71]

102 **Yousaf O**, Stefanopoulou E, Grunfeld EA, Hunter MS. A randomised controlled trial of a cognitive behavioural intervention for men who have hot flushes following prostate cancer treatment (MANCAN): trial protocol. *BMC Cancer* 2012; **12**: 230 [PMID: 22687265 DOI: 10.1186/1471-2407-12-230]

103 **Loprinzi CL**, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994; **331**: 347-352 [PMID: 8028614 DOI: 10.1056/NEJM199408113310602]

104 **Jones JM**, Kohli M, Loprinzi CL. Androgen deprivation therapy-associated vasomotor symptoms. *Asian J Androl* 2012; **14**: 193-197 [PMID: 22286861 DOI: 10.1038/aja.2011.101]

105 **Loprinzi CL**, Dueck AC, Khoyratty BS, Barton DL, Jafar S, Rowland KM, Atherton PJ, Marsa GW, Knutson WH, Bearden JD, Kottschade L, Fitch TR. A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). *Ann Oncol* 2009; **20**: 542-549 [PMID: 19129205 DOI: 10.1093/annonc/mdn644]

106 **Moraska AR**, Atherton PJ, Szydlo DW, Barton DL, Stella PJ, Rowland KM, Schaefer PL, Krook J, Bearden JD, Loprinzi CL. Gabapentin for the management of hot flashes in prostate cancer survivors: a longitudinal continuation Study-NCCTG Trial N00CB. *J Support Oncol* 2010; **8**: 128-132 [PMID: 20552926]

107 **Loprinzi CL**, Pisansky TM, Fonseca R, Sloan JA, Zahasky KM, Quella SK, Novotny PJ, Rummans TA, Dumesic DA, Perez EA. Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. *J Clin Oncol* 1998; **16**: 2377-2381 [PMID: 9667254]

108 **Frisk J**. Managing hot flushes in men after prostate cancer--a systematic review. *Maturitas* 2010; **65**: 15-22 [PMID: 19962840 DOI: 10.1016/j.maturitas.2009.10.017]

109 **Irani J**, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol* 2010; **11**: 147-154 [PMID: 19963436 DOI: 10.1016/S1470-2045(09)70338-9]

110 **Frisk J**, Spetz AC, Hjertberg H, Petersson B, Hammar M. Two modes of acupuncture as a treatment for hot flushes in men with prostate cancer--a prospective multicenter study with long-term follow-up. *Eur Urol* 2009; **55**: 156-163 [PMID: 18294761 DOI: 10.1016/j.eururo.2008.02.002]

111 **Lee MS**, Kim KH, Shin BC, Choi SM, Ernst E. Acupuncture for treating hot flushes in men with prostate cancer: a systematic review. *Support Care Cancer* 2009; **17**: 763-770 [PMID: 19224253 DOI: 10.1007/s00520-009-0589-3]

112 **Park KK**, Lee SH, Chung BH. The effects of long-term androgen deprivation therapy on penile length in patients with prostate cancer: a single-center, prospective, open-label, observational study. *J Sex Med* 2011; **8**: 3214-3219 [PMID: 21699669 DOI: 10.1111/j.1743-6109.2011.02364.x]

113 **Curtis KK**, Adam TJ, Chen SC, Pruthi RK, Gornet MK. Anaemia following initiation of androgen deprivation therapy for metastatic prostate cancer: a retrospective chart review. *Aging Male* 2008; **11**: 157-161 [PMID: 18937151 DOI: 10.1080/13685530802172438]

P- Reviewer: Bao BY, Cihan YB, Simone G, von Eyben FE
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com