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**Functional and metabolic complications of androgen deprivation therapy**

Herrera-Cáceres JO *et al.* Androgen deprivation therapy complications

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**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.

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**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.

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**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](#_ENREF_1)]. Anyhow, incidence of mortality from prostate cancer remains lower than that of lung cancer[[1](#_ENREF_1)].

Patient prognosis depends widely on the risk classification[[2](#_ENREF_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](#_ENREF_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](#_ENREF_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, 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 and Hodges[[5](#_ENREF_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 (RP)[[6](#_ENREF_6),[7](#_ENREF_7)]. Average survival of patients using ADT, with recurrence after primary treatment is 84 mo[[8](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_12)]. A Cochrane Database Systematic Review obtained similar conclusions[[13](#_ENREF_13)].

ADT can have several side effects including new onset diabetes mellitus (DM), osteoporosis, decreased libido, ED, hot flushes, acute kidney injuryand cognitive decline, among others[[14](#_ENREF_14)]. These side effects can occur both with short- and long-term ADT[[7](#_ENREF_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](#_ENREF_15),[16](#_ENREF_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](#_ENREF_17)]. Urologists should consider the evidence based benefits and side effects before initiation of therapy[[7](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_22)]. Also, in a study using the Surveillance, Epidemiology and End Results Program (SEER) database, Kaplan *et* al[[23](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_25)]. In men with prostate cancer, dose of supplementation has not been well established[[26](#_ENREF_26)]. It is recommended that patients should be evaluated with a dual-energy X-ray absorptiometry (DXA) before initiation of ADT[[27](#_ENREF_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](#_ENREF_28)].

ADT has been proven to cause a decreased bone mineral density (BMD), independent of the modality used (either pharmacological or surgical blockade)[[24](#_ENREF_24)]. During ADT, bone remodeling takes place, osteoclast activity seems to be increased whereas osteoblast repair is insufficient[[29](#_ENREF_29)]. Such phenomenon causes decreased BMD and increases bone fracture risk and clinical fractures[[30](#_ENREF_30), [31](#_ENREF_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](#_ENREF_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](#_ENREF_33)]. The longer the time of ADT, the patients have a greater risk of having clinically significant fractures[[34](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_37)].

Patients can be initially treated in a conservative fashion with smoking[[38](#_ENREF_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](#_ENREF_39)], or even before initiation of ADT[[27](#_ENREF_27)]. The use of alendronate (70 mg PO weekly) has showed benefits in patients with prostate cancer and osteoporosis or severe osteopenia[[40](#_ENREF_40),[41](#_ENREF_41)]. For patients with non-metastatic disease, bisphosphonates can keep theBMD stable[[42](#_ENREF_42)].

Denosumab, a human monoclonal antibody against the receptor of the nuclear factor-κβ ligand (RANKL), has proven better in terms of risk of fracture and BMD increase on patients with ADT, compared to placebo[[43](#_ENREF_43),[44](#_ENREF_44)]. Also, in a randomized study with 1904 patients with metastasis and castration resistant disease, denosumab 120 mg subcutaneously was compared against zolendronic acid 4 mg IV. Denosumab was better for prevention of skeletal-events; adverse events were similar for both groups[[45](#_ENREF_45)]. Both, denosumab and zolendronic acid can cause osteonecrosis of the jaw and hypocalcemia[[45](#_ENREF_45)]. Bisphosphonates can cause nephrotoxicity, particularly in patients with chronic kidney failure and also a flu-like condition during the first doses[[28](#_ENREF_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](#_ENREF_46)].

**OBESITY**

Other side effects of ADT are a loss of lean muscle mass and a gain in body fat[[47](#_ENREF_47)], particularly subcutaneous fat[[48](#_ENREF_48)]. It causes a weight gain of about 1.8%-2.4% and an increase in fat body mass by 9.4%-11%[[48](#_ENREF_48),[49](#_ENREF_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](#_ENREF_50)]. Sarcopenia is reported in about 20% of patients with an average lean muscle mass loss of 2.8%[[51](#_ENREF_51)].

Obesity and increased insulin secretion have been related to an increased incidence and more aggressive PCa[[52](#_ENREF_52),[53](#_ENREF_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](#_ENREF_54)]. Obese patients have an increased oxidative stress, predisposing them to the development of several cancers such as endometrial, bladder, breast and prostate[[55](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_17)]. Nevertheless, other large studies have not shown such findings in orchidectomized patients, only showing them in the group receiving GNRH agonists[[56](#_ENREF_56)]. Estimated increased risk using ADT is 16% for CHD, 11% for MI and 16% for SCD[[50](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_59)].

In a multicenter study by Galvao *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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_63)]. The more elements of MetS they have, the greater the risk of PCa[[67](#_ENREF_67)]. Specifically, high blood pressure and high body mass index are the two most relevant factors in terms of PCa death[[68](#_ENREF_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](#_ENREF_63)].

Saylor *et al*[[50](#_ENREF_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](#_ENREF_49),[69](#_ENREF_69)]. Also, patients on ADT do not develop nonalcoholic steatohepatitis[[70](#_ENREF_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](#_ENREF_38)]. The use of metformin along with an exercise program have shown improved outcomes in terms of blood pressure and body weight[[62](#_ENREF_62)]. Metformin can control MetS, but also has an anti-proliferative effect by inhibiting the anabolic stimulation of insulin and activating the AMP-activation protein kinase[[70](#_ENREF_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](#_ENREF_49)]. These side effects are more significant within the first 12 wk of therapy[[71](#_ENREF_71)].

The incidence of diabetes mellitus increases with both, pharmacological and surgical ADT[[17](#_ENREF_17)]. In only 12 wk, glycosylated hemoglobin and fasting plasma insulin levels increase significantly. By the same time, insulin sensitivity decreases[[71](#_ENREF_71)]. There is an increase in glycosylated hemoglobin (HbA1c) of 0.13% after two years of treatment in non-previously diabetic patients[[42](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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 dysglucemia 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](#_ENREF_4)]. Similarly, inflammatory markers such as IGF-1 (which is frequently elevated during ADT), predispose patients to the development of frailty syndrome[[74](#_ENREF_74),[75](#_ENREF_75)].

In a large prospective cohort, Rockwood *et al*[[76](#_ENREF_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 ≥ 3 of the following conditions: weight loss, weakness, fatigue, low activity and slow motion performance with balance and gait abnormalities[[77](#_ENREF_77),[78](#_ENREF_78)]. Also, a “Pre-Frailty” condition has been described in which patients can either develop a full-blown FS or recover[[4](#_ENREF_4),[77](#_ENREF_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](#_ENREF_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](#_ENREF_79)]. Weakness is defined as low grip strength measured with a hand-held dynamometer. Weakness can also be caused by ADT[[80](#_ENREF_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](#_ENREF_74),[81](#_ENREF_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](#_ENREF_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](#_ENREF_77),[83](#_ENREF_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](#_ENREF_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 (IIEF) can be used to standardize results.

First line of treatment is the use of phophosdiesterase 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](#_ENREF_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](#_ENREF_85),[86](#_ENREF_86)]. Fatigue is described in about 40% of these patients[[87](#_ENREF_87)]. With the use of enzalutamide fatigue was reported in 34% of patients (*vs* 29% in the placebo group)[[88](#_ENREF_88)], and with abiraterone 44% (*vs* 43% in the placebo group)[[57](#_ENREF_57)].

Cancer-related fatigue can be improved by aerobic exercise[[89](#_ENREF_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](#_ENREF_90),[91](#_ENREF_91)]. Increased muscle mass and muscle strength can be obtained along with improved quality of life and fatigue[[91](#_ENREF_91),[92](#_ENREF_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](#_ENREF_87)]. Cognitive decline happens in up to 48% of patients on ADT[[93](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_95)].

 Depression diagnosis can be made in a quarter of patients. Nevertheless, such diagnosis cannot be completely attributed to ADT[[51](#_ENREF_51)]. According to a SEER study, ADT by itself does not increase the possibilities of developing depression[[96](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_98)]. The psychological affection in these patients is quite relevant, feeling an impact in masculinity, powerlessness against such symptoms and social embarrassment[[99](#_ENREF_99)]. A classification of the severity of hot flashes is used frequently[[100](#_ENREF_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](#_ENREF_101),[102](#_ENREF_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](#_ENREF_11)] PO or 400 mg intramuscular (I.M.), and megestrol acetate 20-40 mg bid PO][[97](#_ENREF_97),[103](#_ENREF_103)]. This seems to be the most effective therapy[[98](#_ENREF_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](#_ENREF_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](#_ENREF_105),[106](#_ENREF_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](#_ENREF_87)]) and improvement in fatigue, diaphoresis and sleeping trouble[[107](#_ENREF_107)]. Unfortunately, these are mostly from small trials as well as evidence derived from menopausal women[[108](#_ENREF_108)]. Caution should be exercised when using abiraterone acetate since this medication could narrow therapeutic index[[104](#_ENREF_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](#_ENREF_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 (electro-stimulated and traditional[[110](#_ENREF_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](#_ENREF_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](#_ENREF_51)]. Penile length decrease of > 1 cm was reported by 93% of patients in one study[[112](#_ENREF_112)]. A hemoglobin decline of -1.11 g/dL (normocytic normochromic) has been reported, and most patients are asymptomatic[[113](#_ENREF_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.

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