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Androgen Deprivation Therapy for Prostate Cancer

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1. Introduction

Since 1941, when Huggins and Hodges proved the favourable effect of surgical castration and oestrogen administration on the progression of metastatic prostate cancer (PCa) (1,2), androgen deprivation therapy (ADT) became the mainstay of management of advanced PCa till now. They demonstrated for the first time the responsiveness of PCa to androgen deprivation.

ADT effectively palliates the symptoms of advanced disease, significantly reduces tumor growth, but there is no conclusive evidence at present that it prolongs survival. Moreover, significant amount of data report that ADT is associated with several adverse effects. The most prominent include: loss of bone mineral density (BMD), which leads into increased fracture risk (3), induction of insulin resistance (4), unfavorable changes in serum lipid profile (5), changes in body composition (6) which can lead into increased cardiovascular morbidity (7) and changes in cognitive functions (8).

The aim of ADT is to cause severe hypogonadism, and adverse effects of ADT clearly demonstrate the essential and pluripotent role of male´s most important androgen – testosterone (TST).

2. Testosterone: A basal overview of biosynthesis, metabolism and its action

In the human male, the main circulating androgen is testosterone (TST). More than 95% of circulating TST is secreted by the testis (Leydig cells) which produce aproximately 6-7 mg of TST daily (9). The rest is secreted by the adrenal cortex, and very small quantities (especially pregnan derivatives) are formed by the cells of the brain (10).

Physiologic TST level in a male is 3-8 ng / ml. The source for the synthesis of steroids is cholesterol. This substrate may be synthetized *de novo* from acetate but it may be also taken up from plasma lipoproteins. Cleavage of the side chain of cholesterol in the mitochondria and the formation of pregnenolone (biologically inactive) is the start of steroidogenic cascade. Pregnenolone is further converted into various steroids by enzymes (cytochromes P450) in the endoplasmatic reticulum.

TST secretion is regulated by the hypothalamic-pituitary-gonadal axis. The hypothalamic luteinising hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH). The main regulator of Leydig cell function is LH, acting through the LH receptor (LHr) in Leydig cells.

LH and FSH are required for the development and maintance of testicular functions.The natural ligand for the LHr is LH, but also human choriogonatropin (hCG) can equally well activate the LHr. Activated LHr stimulate adenylyl cyclase via GTP binding proteins and this results in increased production of cyclic AMP (cAMP). cAMP increases steroid production (11).

The total concentration of steroids in target tissues (central and peripheral nervous system, bone, muscle, adipose tissue, haematopoetic system and myocardium) and body fluids is dependent on the presence of binding proteins (sex hormone binding globulin, SHBG, albumin). Binding proteins represent a storage form of circulating steroids, which bind 98% of circulating TST. The rest-2% is "free testosterone" (fTST), which is biologically active. Homeostasis is achieved by "closed" steroid feedback inhibition mechanism, where the plasmatic level of steroids affects the secretion of LH from adenohypophysis.

The effect of TST on target tissues is modulated by metabolic pathways.

1. *Aromatisation* of TST gives rise to 17b- estradiol. When the target cell is estrogen-dependent, the aromatase activity in target cells and supply of androgen substrate (TST) are of major importance for determining the rate of synthesis of estrogens. Aromatase cytochrome P450 enzyme is expressed in many tissues including placenta, ovary, testis, fat tissue, liver, brain, hair follicles.
2. *Reduction* of TST into 5-alfa-dihydrotestosterone (DHT) is achieved by 5a-reductase. This active form of TST (5 to 10 times more biologically effective) can fully activate the androgen receptor (AR) (12). There are 3 isoforms of 5a-reductase. Isoform 2 is clinically more important because its deficiency is associated with distinct clinical manifestations (13). Isoform 2 predominates in cells of the prostate and external genitalia, while isoform 1 predominates in the cells of the skin (except genitals), and in liver cells in small amounts. However, in prostate cancer cells, overexpression of isoform 1 is a common finding, thus increasing its clinical significance (14). In the total deficiency of isoform 2 (autosomal recessive) there is a serious alteration of the development of sex organs in utero (male pseudohermafroditism). Many mutations of the gene encoding isoform 2 are known and can result into a number of different clinical manifestations. Signs of its deficiency are small phallus, severe hypospadias, scrotum bifidum, residual prostate utriculus (15). The newly discovered isoform 3 may play an important role in the development of hormone-refractory prostate cancer (HRCaP) as its overexpression is found in the HRCaP cells (16).

In addition to these metabolic pathways, the level of DHT in target tissues is affected by other enzymes (hydroxysteroid dehydrogenases), which "fine-tune" the effect of androgens in the target tissues (17). Owing to these local conversions the peripheral plasma concentration of androgens are only a rough indicator for their biological activities (12).

The mechanism of action of androgens can be divided into genomic and non-genomic effect (12). Non - genomic effects of androgens include mechanisms affecting the flow of calcium in the cells and the effect on phosphorylation cascade of Map-kinase (18, 19), or membrane effects (20). Genomic effects are mediated by activation of androgen receptor (AR). AR acts as a transcription factor activated by its ligand (TST). By androgen binding, AR is translocated from the cytoplasm to the nucleus where it binds to its DNA domain and interacts as a homodimer with specific DNA sequences that are referred as androgen responsive elements (ARES) (21). Its binding to DNA leads into interactions with transcription factors (22) and other co-factor proteins (21). This results into the "up" or "down" regulation of transcription of target genes (23).

Androgen metabolites are excreted as free steroids or bound (conjugated). Conjugated steroids are bound to glucuronide or sulfate group. Androgens are mostly degraded in the liver (glucuronate, sulphates), but the prostate the skin also contribute significantly to the metabolism of androgens. All the steroid - metabolising enzymes constitute a network for transforming androgens into secretion products (conjugated, unconjugated) that finally leave the body via the urine or the skin. The flux though this network is great, because the half-life of TST in men is only 12 minutes (12).

3. Androgens and bone metabolism

Growth and resorption of bone tissue are mediated by *osteoblasts* and *osteoclasts*. Both types of cells exert mutual influence on each other and equilibrium between the activity of both cell lines maintains net bone mass during constant renewal and turnover. Decreased osteoblast activity and increased activity of osteoclasts leads into loss of bone mass. AR have been located on normal human osteoblasts (24) and both aromatizable and non-aromatizable androgens can stimulate of human osteoblasts proliferation in vitro (25).

Bone deformation strain represents a stimulus for osteoblastic activity. Androgens modify the effects induced by the mechanoreception of human osteoblastic cells by affecting adhesion molecule expression, i.e. fibronectin and the fibronectin receptor. These substances facilitate the adhesion of bone cells to the extracellular matrix, which represents a crucial requirement for osteoblastic development and function (26). In addition, the secretion of osteoprotegerin (OPG), which is unaffected by mechanical strain alone, is doubled when this stimulus occurs in the presence of androgens. OPG is a decoy receptor for RANKL (receptor activator of nuclear factor-kappaB ligand). RANKL is secreted by osteoblasts, it induces osteoclastogenesis stimulates osteoclast differentiation (27). Thus, OPG inhibits bone resoptive effect induced by RANKL (26). Accordingly, TST levels directly correlate with OPG concentrations in healthy men (28).

Parathyroid hormone (PTH) induces osteoclast formation a differentiation. Androgens have direct inhibiting effect on this process via osteoclasts, which express AR and these cells are also blocked form PTH effects by androgens when no conversion to estrogens occurs (29).

Androgens decrease the number of bone remodeling cycles by modifying the genesis of osteoclasts and osteoblasts from their respective progenitor cells. In addition, androgens also exert effects on the lifespan of mature bone cells: they exert pro apoptotic effects on osteoclasts and anti-apoptotic effects on osteoblasts and osteocytes. TST also modulates effects induced by other hormones and cytokines involved in bone metabolism (30).

Osteoblast activity is reflected by concentration of procollagen type 1 (carboxy-terminal: P1CP or amino-terminal: P1NP) and other non collagenous proteins secreted by osteoblasts, eg. osteocalcin and bone specific alkaline phosphatase (BSAP). Also OPG as a decoy receptor for RANKL, can serve as marker of osteoblast activity. Bone resorption, hence osteoclast activity, therefore, can be estimated by urinary excretion of degradation products of type I collagen, such as deoxypyridinoline (DPD) and collagen type I cross- linked N-telopeptide (NTX) (31).

An independent role of androgens in protecting bone mass, both by promoting bone formation and attenuating bone resorption has been demonstrated in humans. Nevertheless, the role of its metabolite estradiol is pivotal in bone metabolism (30).

Aromatization of TST to estradiol is a pivotal event concerning effects of sex steroids on bone metabolism. Estrogen receptors (ER) have been localized in human osteoblasts (32),

osteoclasts (33), and osteocytes (34). Human males with mutations of ER or aromatase genes do not achieve normal bone density, despite normal or increased levels of serum TST (35).

4. Androgen deprivation therapy (ADT) and its side effects

ADT is increasingly attained through the use of luteinizing hormone-releasing hormone (LHRH) agonists, which down-regulate anterior pituitary receptors and lead to therapeutic hypogonadism, or directly by inhibiting pituary receptors by LHRH antagonists. The standard castration level is < 50 ng/dL. Prostate cells are physiologically dependent on androgens which stimulate its growth, function and proferation. TST, although not tumorigenic, is essential for the growth and perpetuation of tumor cells (36).
Prostate cancer (PCa) displays a range of clinical behavior, from slow-growing tumors of no clinical significance to aggressively metastatic and lethal disease. Most PCa cases diagnosed with present diagnostic techniques fall into the moderately differentiated group (grade 2, Gleason 6), of which the cancer-specific 10–15-year mortality is 18–30%. This is even lower in the group of PCa diagnosed with grade 1 and 2 or Gleason 4–6, and there are subgroups of patients who are not at risk of dying from PCa even within 15years. Overall mortality is then determined by comorbidity (37). While both short- and long-term ADT are effective for treating PCa, it can often have significant side-effects. It is important that these complications are recognized and managed appropriately so that adverse effects on the patient's quality of life (QoL) are minimized. There has been an increase in the use of ADT at all stages of PCa in recent years. The extensive use of ADT is raising concerns about adverse effects – loss of BMD being the most prominent.

5. Bone loss and osteoporosis

As shown above, androgens are important for maintenance of bone tissue. Although ADT is used in medical practice for more than 60 years, it's only few years that the clinicians became aware of serious and potentially catastrophic consequences resulting form long-term ADT.
Bone density is determined both by peak bone mass achieved during skeletal development and the subsequent amount of maintenance and resorption of bone tissue. Androgens affect both processes and thus are a pivotal determinant of bone mass in men.

5.1 Osteoporosis

Osteoporosis is defined as a systemic metabolic bone disease characterized by low bone mass density (BMD) and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (38). Diagnosis of osteoporosis based on WHO definitions is developed for women originally (39). When based on male cutoffs, 1-2 million (3 - 6%) of men have osteoporosis and 8 -13 million (28 - 47%) have osteopenia; when based on female cutoffs, 280,000 - 1 million (1 - 4%) have osteoporosis and 4 - 9 million (15 - 33%) have osteopenia (40, 41). While this numbers may seem disturbing, it is believed that osteoporosis in men is substantially underdiagnosed and undertreated in the United States (42).
Female osteoporosis has been studied extensively and characterized due to its high prevalence (43) whereas male osteoporosis, especially that associated with ADT has gained focus only recently.

In men, osteoporosis occurs later than in women (44), but the prevalence of osteopenia does not differ significantly between men and women aged more than 50 years. Conversely, the prevalence of osteoporosis in men is lower than in women (40). Even though it may be underestimated when standard female BMD parameters are considered suitable for normal mineralization in men (45). Men generally have a higher BMD than women at the same age (46). Accordingly, the prevalence of male osteoporosis is greater when male-specific ranges are used in men above fifties: ranging from 1% to 4% of elderly men when the diagnosis is based on female cut-off points vs. 3% to 6% when based on male cut-off points (40).
Men are estimated to lose bone mineral density (BMD) at a rate of up to 1% per year with advancing age (47, 48), and one in eight men over age 50 years will experience an osteoporosis-related fracture in their lifetime (49). Of all osteoporotic fractures, hip fractures contribute to the greatest morbidity as well as mortality, both of which are much greater in men than in women (50-52).

5.2 Diagnosis of osteoporosis

Current guidelines recommend assessment of bone mineral density (BMD) previous to ADT and yearly thereafter (53) with dual-energy x-ray absorptiometry (DXA) which is considered the standard method to measure BMD (54). International Society for Clinical Densitometry (ISCD) recommends that central skeleton sites (lumbar spine, total hip and femoral neck) are the most appropriate locations to asses BMD (55).
Diagnosis of osteoporosis can than be made according to WHO classification: if T- score is less than 2,5 of standard deviation. Values between (-) 1 and (-) 2.5 SD (standard deviation) is defined as osteopenia. T - score stands for the number of standard deviations (SD) from the density of young healthy individuals of the same sex (39).(Table 1)
To improve the identification of patients at highest risk of fracture, WHO has developed an algorithm to predict fractures - FRAX ™ http://www.shef.ac.uk/FRAX/
According to European Association of Urology (EAU) guidelines, a precise evaluation of BMD should be performed by dual X-ray absorptiometry before starting long-term ADT. An initial low BMD (T-score below 2.5, or below 1 if other risk factors are present) indicates a high risk of subsequent non-metastatic fracture, suggesting the need for early use of preventive bisphosphonate therapy (56).

Clasiffication	T-score
Normal	>-1
Osteopenia	-1 - -2,5
Osteoporosis	<-2,5

Table 1.

5.3 ADT, prostate cancer (PCa) and clinical aspects of bone disease

At presence, significant amount of data report that ADT is associated with the loss of BMD in a time-dependent manner (57-59) which leads into increased fracture risk (60). Skeletal fractures negatively correlate with overall survival in men with PCa (61) and maintaining skeletal health is crucial for QoL and survival (62).
Treatment of complications of pathological fractures is complicated and expensive (63). Moreover, the typical feature of PCa is the ability to metastasize into bone in more than 80 % of cases (64). Most bone lesions in PCa are osteoblastic in nature (65). However, studies

show that osteoblastic lesions in PCa have excessive bone growth, but on the other hand also simultaneously increased osteolysis (66). The new bone formed by tumor stimulated osteoblast is weak and poorly mineralized and subsequent osteopenia leads into increased osteolysis - result to the creation of bone matrix with seriously compromised integrity. The risk of developing bone complications is therefore increased.

Treatment of PCa does not focus on skeletal complications that may arise from bone metastases. The main symptom of bone metastases is severe bone pain, which often requires strong narcotic therapy or palliative radiation therapy. Other complications include spinal cord compression and pathological fractures, which may require surgery. These skeletal complications have a negative effect on QoL (65).

Data from a double-blind, placebo-controlled studies show that approximately half of patients treated with ADT had one or more events associated with the skeleton. Most of these events required palliative radiotherapy, or were pathological fractures (67). Skeletal complications are also associated with significant financial expenditure. A recent analysis of the costs of health insurance in the U.S. since 1994 until 2002 revealed that the total cost to treat patient with PCa who had skeletal event were 20 000 dollars higher than in patient who did not experience skeletal event (68).

Interestingly, it has been reported that hormone naive patients with advanced PCa have lower baseline BMD than healthy control, and relatively high prevalence of osteopenia and osteoporosis (69, 70). The largest study that investigated the association of BMD measures with PCa risk in older men enrolled was the Osteoporotic Fractures in Men Study (MrOS) (71).

MrOS was prospective study conducted on 4597 men with mean follow up 5.2 years, which evaluated the association of BMD and incidental PCa in a cohort of older men with no history of PCa. Unexpectedly, the authors found that higher total body BMD was significantly related to reduced risk for PCa. This result was „unexpected" because authors presumed that the higher levels of androgens lead into higher prevalence of PCa, which positively correlates with BMD. Additionally, total body BMD was inversely associated with the development of high-grade, but not low-grade disease. A similar but weaker association was observed for total hip BMD with high-grade PCa. This study confirms the association, although still not elucidated, between low BMD and PCa.

5.4 Treatment of ADT induced osteoporosis

Lifestyle changes: Immobilization is an important cause of bone loss. Immobile patients lose bone mass more rapidly than mobile patients. Regular daily activities, overcoming gravity, walking, and exercise have a positive impact on bone density: it stimulates osteoblasts to produce new bone and inhibits osteoclasts, thereby decreasing resorption of bone. It also improves physical coordination (prevention of falls). Cessation of smoking, decreased alcohol consumption and normalization of body mass index (BMI) helps to maintain BMD (72).

Ca supplementation: The ideal is to ensure that the amount of calcium is taken in the normal diet. If the patient is unable to take the recommended amount of calcium in the diet (lactose intolerance, hyperlipoproteinemia, etc) it is recommended for calcium supplementation (1000mg – 1500 mg daily) (72).

Vitamin D: Supplementation of vitamin D is recommended when its deficiency can be assumed or proven. The recommended daily dose is 400-800 IU (10-20 mg).

Bisphosphonates are one of the most potent inhibitors of bone resorption. The effect on the reduction of osteoporotic fractures has been demonstrated for treatment with alendronate, risedronate, ibandronate, etidronate and zoledronic acid. The effectiveness in reducing vertebral and nonvertebral fractures were confirmed by many studies (73, 74, 75). The optimal regimen for zoledronic acid is unclear, because one study recommends treatment every 3 weeks (76), while another trial has produced similar results with an annual injection (77), and finally, another study reports that single infusion of zoledronic acid in patients receiving ADT reduces bone mineral loss and maintains BMD at least for 12 months during ADT (78).

One of the most important and serious adverse effect of bisphoshonate administration is jaw necrosis (79) The initial BMD could be used to guide the choice of regimen (80).Thus, a 3-month injection might be given in osteoporotic patients, for whom a yearly injection is likely to provide insufficient protection (56).

Denosumab is a fully human monoclonal antibody against RANKL (see above). In the largest, well conducted study to date, denosumab was associated with 5.6% increase in the lumbar BMD versus 1% decrease in the placebo arm. There were also significant BMD increases at the total hip, femoral neck and distal third of the radius. 60 mg was delivered subcutaneously every 6 months, was not associated with any significant toxicity, or delayed healing in vertebral fractures (81).

6. Androgens and cognitive functions

It is known that during certain developmental stages- especially during the first years of life, during adolescence, girls surpass in boys several verbal skills. Males excel after about the tenth year of life in non-verbal skills in adulthood, especially in spatial orientation and manipulation (82).

Evidence of a link between sex hormones and spatial abilities came from studies of individuals with Turner syndrome (XO karyotype, no gonadal hormones) or testicular feminization syndrome- (XY karyotype, the tissues are refractory to normal levels of TST). These patients have female external genitalia, they are raised as girls. In these patients verbal skills surpass their spatial abilities, which is a typical pattern of cognitive abilities of women (83).

Studies on men with idiopathic or acquired hypogonadotrophic hypogonadism confirm the importance of TST for spatial abilities. Short-term androgen supplementation did not restore spatial function, suggesting that low levels of sex hormones during the intrauterine and neonatal period have a lifelong impact (84).

Direct sex hormones manipulation supports the conclusion that androgens play an important role in cognition. The first experiments with direct hormonal manipulation can be traced back to 1941 when Simonson et al. (85) published their experiment using methyl TST that was administered to eunuchoids, castrated males, and elderly men. The result was an improved ability to perceive the flicker (critical flicker frequency), a measure of attention and alertness, as long as the androgen treatment lasted (86).

Androgen therapy was also administered to female to male transsexuals in high doses as a preparation before gender reassignment. Their spatial skills have significantly improved, while verbal skills declined considerably (87).

For ethical reasons, nowadays the manipulation of gonadal hormones is restricted to patients in clinical studies. Thus, the last such study was conducted in 1971. Klaiber et al. (88) studied the effect of infused TST on mental abilities in healthy male students. After a 4-

hour infusion of TST or saline in the control group, performance of the control group (saline infusion) showed a significant decline in mental performance when compared to TST infused group.

6.1 Potential mechanisms of action

TST may impact cognition through several mechanisms. For example, activation of calcium channels in the brain occurs through rapid, nongenomic methods of action on G-protein-coupled, agonist sequestrable testosterone membrane receptors that initiate a transcription-independent signal pathway (89). TST also may impact cognitive performance directly through modulating neurotransmitters and stimulating neuronal connectivity, decreasing β-amyloid peptide production, and preventing N-methyl-D-aspartate excitotoxicity (90) mechanisms implicated in cognitive disorders such as Alzheimer disease or dementia. Furthermore, some estrogen studies have highlighted several possible mechanisms through which this hormone can impact cognitive functioning (91). These include increasing cholinergic activity through its action of choline acetyltransferase, maintenance of dendritic spine density on CA1 pyramidal cells of the hippocampus and facilitating induction of long-term potentiation in the hippocampus, increasing serotonergic and cholinergic activity to maintain neural circuitry, altering lipoprotein, and decreasing risk of cerebral ischemia (92, 93).

6.2 Cognitive functions and ADT

Green et al were the first to systematically research the impact of androgen-ablation therapy on the cognitive functioning of men with PCa. Sixty-five men (mean age, 73 years) with advanced PCa were assigned randomly to 1 of 4 groups: leuprolide (N = 19), goserelin (N = 20), cyproterone acetate (N = 11), and monitoring without hormone treatment (N = 15). All men participated in a battery of neuropsychological assessments at baseline (ie, 1 week before treatment) and then 6 months later. PSA and TST levels decreased significantly from baseline to 6 months for the 3 hormonally treated groups. Conflicting results emerged in the memory domain; men in the goserelin group surprisingly improved on 2 measures of memory (verbal [Wechsler Memory Scale-Revised] and visual [Rey-Osterrieth Complex Figure test]) but declined in another measure of verbal memory (Auditory Verbal Learning Test). The goserelin group also declined in a measure of executive functioning (Trails B). Of the 50 men on active treatments, 24 men showed a reliable decline (ie, >1 standard deviation) on at least 1 cognitive task, and 7 men showed a reliable change on 2 tasks, whereas the monitoring-only group showed no decline on any of the tasks (94).

Salminen et al researched the cognitive effects of ADT on 26 men who were diagnosed recently with PCa and who began ADT 2 months before radiotherapy. From baseline to 12 months, tests of visuomotor speed and of reaction time saw significant decreases. The decline in TST coincided with a decline in visuomotor processing (digit symbol), reaction time (10-choice reaction time), working memory speed (subtraction), sustained attention (vigilance), and recognition speed (recognition of letters) (95).

Jenkins et al assessed 32 men with standard neuropsychological assessments at 3 time intervals: at baseline, 3 months, and 9 months. The average age of these men was 67.5 years, and they used ADT for 3 to 5 months. Twenty-five healthy men, similar in age, served as the control group. Although there was no overall group effect, a greater percent of men in the ablation group reported a significant cognitive decline in 1 task (47%)

compared with the control group (17%; odds ratio, 4.412; P < .05) at the 3-month time point. There were no significant differences between the groups at the 9-month time point. On specific domain analysis, the tasks most impacted at the 3 month time point were spatial memory and ability (96).

Joly et al compared physical and cognitive function in a cross-sectional study of 57 patients who were receiving ADT for nonmetastatic PCa and 51 healthy, age-matched controls. Thirty patients received ADT as adjuvant treatment after prostatectomy or radiotherapy, and 27 patients received ADT for increasing levels of PSA. The median duration on ablation therapy was 1.8 years (range, 0.4-7.4 years). To assess cognitive functioning, the researcher administered the Sensitivity Cognitive Screen and a self-reported assessment on cognitive deficits (the Functional Assessment of Cancer Treatment-Cognitive Scale [FACT-COG]). In contrast to other studies cited above, Joly and colleagues observed that, although men with nonmetastatic PCa who received ADT experienced more treatment-related symptoms, no differences in cognitive function on either the High Sensitivity Cognitive Screen or the FACT-COG. The authors suggested that the High Sensitivity Cognitive Screen may not be sensitive enough to detect the subtle cognitive changes that occur after ADT. In addition, self-report of cognitive function has not been correlated consistently with actual neuropsychological testing (97).

In conclusion, the data show that androgen ablation does have cosequences for cognitive functioning. Larger longitudinal studies are warranted.

6.3 ADT and changes in body composition

Male hypogonadism (of any etiology) results in a decline in lean body mass (LBM) and an increase in fat mass, which is reversed with TST replacement (98). A cross-sectional study showed that men undergoing long-term ADT (12–101 months) have increased fat mass in the trunk and all extremities- measured by dual-energy x-ray absorptiometry (DXA), compared with eugonadal men with PCa not undergoing ADT (treated with prostatectomy and/or radiation therapy) and age-matched eugonadal controls (99).

Another case control study examined the prevalence and magnitude of obesity and fat mass in a group of 62 men with PCa receiving ADT for 1–5 yr (100). Healthy men (n = 47) with a PSA of less than 4.0 ng/ml were recruited as controls. The study showed that men with PCa had significantly higher body weight (86.5 vs. 80.6 kg) and percent body fat (30 vs. 26%) than controls.

Meta-analysis of sixteen studies showed that ADT increased percentage of body fat by on average 7.7% (95% CI 4.3, 11.2, from seven studies, P < 0.0001) and decreased % LBM by on average -2.8% (95% CI -3.6, -2.0, from six studies, P < 0.0001) but for both there was marked heterogeneity between studies (I2 = 99% I2 = 73%, respectively). Similarly, body weight (2.1%, P < 0.0001 from nine studies) and BMI (2.2%, P < 0.0001, from eight studies) increased significantly. More extensive changes were seen with longer duration of treatment (101).

These studies prove that ADT results in an unfavorable body composition. The increase of fat mass in patients on ADT correlates positively with rising insulin levels (102). Hence, this increasing adiposity may be the primary event leading to these metabolic complications (possibly via elaboration of adipokines and inflammatory cytokines). Similarly, it is possible that a decrease in muscle mass may result in decreased glucose uptake by the muscle. These changes may ultimately lead to insulin resistance and diabetes in this population, hence

predisposing them to cardiovascular disease. Lifestyle changes or suitable interventions to minimize the effect of ADT on body composition need to be investigated.

7. ADT and insulin resistance

Epidemiological studies have shown that low TST levels predict the development of insulin resistance and type 2 diabetes (103, 104, 105). Studies have also confirmed a direct relationship between serum TST and insulin sensitivity (106). These findings are further supported by interventional studies showing an improvement in insulin sensitivity with TST replacement in hypogonadal obese men (107).

7.1 Early metabolic changes

There is some evidence, that the onset of insulin resistance can be detectable after 3 months of ADT (108, 109). 3-month prospective study using combined androgen blockade with leuprolide and bicalutamide showed a 43% increase in fat mass and a 26% increase in insulin levels from baseline, again indicating development of insulin resistance with increasing adiposity (110). Although there was no significant change in fasting glucose levels, a statistically significant increase in glycosylated hemoglobin was seen (though this increase was within the normal range from 5.46–5.62%). These observations suggest that insulin resistance develops within a few months of initiating ADT; however, this compensatory hyperinsulinemia prevents the development of diabetes.

7.2 Late metabolic changes

Observational study of a population-based cohort found that men undergoing ADT with GnRH agonists had a higher risk of incident diabetes (11%), coronary artery disease (25%), myocardial infarction, and sudden death (111). Interestingly, orchiectomy was associated only with a higher risk of diabetes. In some men, this risk was evident within 4 months of starting ADT. These findings suggest that although both medical and surgical modalities of ADT result in increased metabolic burden, GnRH analogs are also associated with cardiovascular events.

After 12 months of ADT, serum fasting glucose increased significantly (112), suggesting that men with PCa who are receiving long-term ADT are at risk for developing insulin resistance and hyperglycemia, thus leading to their increased risk of cardiovascular disease (113).

A retrospective study which enrolled 396 patients with a median follow-up of 60.1 months, 36 (11.3%) patients developed new- onset diabetes mellitus (NODM). In 77 patients with pre-existing diabetes, there was an increase of >/=10% in serum HbA1c or fasting glucose levels in 15 (19.5%) and 22 (28.6%), respectively. On multivariate analysis, a BMI of >/=30 kg/m(2) was associated with an increased risk of developing NODM (odds ratio 4.65, P = 0.031) (114).

In conclusion, patients receiving ADT for PCa with or with no history of diabetes should have routine surveillance of glycaemic control, with appropriate preventive and treatment measures.

8. ADT and lipid alterations

Hyperlipidemia is a known risk factor for cardiovascular disease. Recent epidemiological research suggests that low serum TST levels in men are associated with an adverse lipid

profile, especially elevated total cholesterol, LDL cholesterol, and triglycerides (115). Furthermore, interventional studies have shown that TST replacement in hypogonadal men results in an improvement in lipid profile (116).

During long-term ADT, triglycerides rise by approximately 26% and total cholesterol approximately 10%. (117, 118, 119) In addition, high-density lipoprotein (HDL) rises approximately 8% to 11%. The net effect of these changes on cardiovascular risks is unknown. Significant changes can be observed within the first 3 months of treatment, with more modest subsequent change (110).

9. ADT, metabolic syndrome and cardiovascular disease

Metabolic syndrome (MS) is a known risk factor for cardiovascular disease (CVD) (120). According to the Adult Treatment Panel III guidelines (121), a man is considered to have MS if he meets 3 of the following 5 criteria: fasting plasma glucose level >110 mg/dL, serum triglyceride level 150 mg/dL, serum high-density lipoprotein level <40 mg/dL, waist circumference >102 cm, and blood pressure ≥ 130/85 mmHg. Subjects on antihypertensive and antilipid medications are also considered positive for the respective criteria. Recently, male hypogonadism has surfaced as an independent risk factor for MS. Cross-sectional studies have shown that men with hypotestosteronemia have a higher prevalence of MS (122). Longitudinal studies also show that lower androgen levels in men independently predict the development of MS (105).

These observations suggest that profound hypogonadism due to ADT imparts increased metabolic burden. Long-term prospective studies are needed to determine the time of onset of various metabolic alterations in these men.

Since MS is associated with CVD, large studies were conducted to assed the CV risk and ADT. A large SEER-Medicare–based analysis of 73,196 men aged 66 years and older with PCa identified significant GnRH agonist-associated elevations in risk for myocardial infarction (HR, 1.11; p= .03), sudden cardiac death (HR, 1.16; p = .004), and new diagnosis of coronary heart disease (HR, 1.16; p< .001) (123). Similarly, a second SEER-Medicare–based study of 23,000 men with PCa found a 20% ADT-attributable rise in CV morbidity at 1 year (124).

In contrast, a recently reported matched cohort analysis of approximately 20,000 men in an On-tario database found no association between ADT and acute myocardial infarction (HR, 0.91; 95% CI, 0.84–1.00) (125).

A smaller population-based observational study of 3262 men who had undergone prostatectomy for PCa found that ADT was significantly associated with CV mortality, although only in the subset of men aged 65 years and older (126). This analysis failed to validate baseline coronary artery disease and diabetes as risk factors for CV mortality. Finally, combined analysis of 3 randomized trials involving men with localized PCa found that in the subset of men aged 65 years and older, 6 months of treatment with a GnRH agonist led to earlier onset of fatal myocardial infarction (127).

Three large randomized, controlled trials by the Radiation Therapy Oncology Group (RTOG) have been retrospectively analyzed for an association between neoadjuvant/ concomitant/adjuvant ADT and CV mortality. These analyses have not found convincing evidence of an association (128-130). Secondary analyses of a randomized controlled trial from the EORTC found no association between ADT and CV mortality. The RTOG and EORTC trials were randomized, featured large enrollments, and had long-term follow-up.

Bone metabolism	Loss of BMD, skeletal events (fractures), increased morbidity&mortality
Bone marrow	Anaemia
Lipid profile alterations	Increased: overall cholesterol, TAG, LDL, HDL
Impaired insuline sensitivity	Hyperinsulinemia, new onset diabetes, worsening existing DM
Body composition	Increase in fat mass, decrease in muscle mass, increased BMI
Cardiovascular disease	Increased risk of CV morbidity and mortality (?)
Metabolic syndrome	See above
Cognitive functions	Impaired spatial cognition, reaction time, other (?)
Other	Mood changes, loss of libido

Table 2. Summary of main organ systems affected by severe hypogonadism (by ADT)

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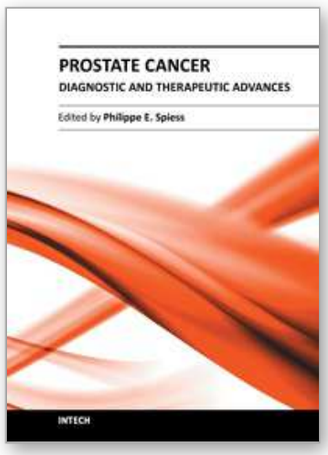
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Prostate Cancer - Diagnostic and Therapeutic Advances
Edited by Dr. Philippe E. Spiess

ISBN 978-953-307-319-4
Hard cover, 378 pages
Publisher InTech
Published online 25, November, 2011
Published in print edition November, 2011

In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book , readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade.This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

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Stanislav Ziaran (2011). Androgen Deprivation Therapy for Prostate Cancer, Prostate Cancer - Diagnostic and Therapeutic Advances, Dr. Philippe E. Spiess (Ed.), ISBN: 978-953-307-319-4, InTech, Available from: http://www.intechopen.com/books/prostate-cancer-diagnostic-and-therapeutic-advances/androgen-deprivation-therapy-for-prostate-cancer

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