SEX LIFE IN PATIENTS WITH METASTATIC PROSTATE CANCER ON ANDROGEN DEPRIVATION THERAPY

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ABSTRACT

Prostate cancer is the most common cancer affecting men. Androgen deprivation therapy (ADT) is accepted as the primary treatment modality of advanced or metastatic prostate cancer. Erectile dysfunction and loss of libido are well-known side effects of ADT. In the previous studies, androgens have been demonstrated to play an important role in erectile physiology. However, the molecular mechanisms involving this issue have not been completely understood yet. The objective of this review is the assessment of ADT's effects on sexual functions in light of the current literature.

Keywords: *Prostate cancer, testosterone, erectile dysfunction, libido.* ***Nobel Med 2015; 11(2): 5-12***

ANDROJEN DEPRİVASYON TEDAVİSİ ALAN METASTATİK PROSTAT KANSERLİ HASTALARDA CİNSEL YAŞAM

ÖZET

Prostat kanseri erkekleri en sık etkileyen kanser türüdür. Androjen deprivasyon tedavisi (ADT) ileri evre ve metastatik prostat kanserli hastaların tedavisinde ilk sırada yer almaktadır. Erektil disfonksiyon ve libido kaybı ADT'nin bilinen yan etkileridir. Androjenlerin yapılan çalışmalarda erektil fizyolojide önemli rol oynadığı gösterilmiştir. Fakat bu konudaki moleküler mekanizmalar hala tam olarak anlaşılamamıştır. Bu derlemede ADT alan hastalardaki seksüel fonksiyonların literatür ışığında değerlendirilmesi amaçlanmıştır.

Anahtar kelimeler: Prostat kanseri, testosteron, erektil disfonksiyon, libido. **Nobel Med 2015; 11(2): 5-12**

INTRODUCTION

Prostate cancer, is the leading neoplasm among men with an incidence of 214/1000.[1,2] Prostate cancer is the second most common cause of death among the cancer related deaths. The average age at the time of diagnosis is 68 years and 63% of the patients diagnosed with prostate cancer are aged above 65 years.[3]

Androgen deprivation therapy (ADT) is accepted as the primary treatment modality of advanced or metastatic prostate cancer. In addition, this therapy may be used as a primary therapy in patients with positive lymph nodes, in combination with radiation therapy, in the cases of biochemical recurrence after the first line treatment.[4,5]

The hormonal therapy of prostate cancer includes medical (LHRH agonists, antagonists) or surgical castration, antiandrogens and adrenal androgen inhibitors. Hormonal therapy may administered in different modalities: Early or delayed, combination, intermittent, neoadjuvant or adjuvant modalities.

Erectile dysfunction and loss of libido are well-known side effects of ADT and they were first described by Huggins et al. in 1941. Huggins et al. reported loss of libido and erectile dysfunction in 21 patients who had underwent castration for prostate cancer.[6]

Erectile dysfunction has a negative impact on the quality of life of both the patient and his partner.[7,8] In the previous studies, androgens have been demonstrated to play an important role in erectile physiology. However, the molecular mechanisms involving this issue have not been completely understood yet and there is a lack of human studies in this field.[9] Although the ADT results in sexual dysfunction in the majority of patients, the preservation of sexual activity in the remaining 20% of

the patients has not been explained.[10,11] The objective of this review is the assessment of ADT's effects on sexual functions in light of the current literature.

Androgens and Sexual Functions

The male sexual activity depends on libido increase and synchronous penile tumescence. Testosterone (T) is important for the regulation of the sexual functions due to its influence on both central and peripheral pathways.[12]

Testosterone is synthesized from cholesterol in the Leydig cells, testicular interstitial cells.[13] Cholesterol is transported to the inner mitochondrial membrane via 2 proteins called acute regulatory protein and peripheral benzodiazepine receptor. Here, 3β-hydroxysteroid dehydrogenase, cytochrome P450, 17α-hydroxylase / C17-20 lyase and 17 β-hydroxysteroid dehydrogenase are involved in the biosynthesis of T via Δ4 and Δ5 pathways.

Although frontdoor pathway, the biosynthesis of dihydrotestosterone (DHT), an active metabolite of T, has been known to take place via Δ4 and Δ5, an alternative backdoor pathway of DHT synthesis that bypasses T, was also shown recently.[14,15]

The backdoor pathway consists of the conversion of dihydroprogesterone-to dihydrotestosterone in the sequence of dihydroprogesterone- allopregnanolone-17-OH allopregnanolone- androsterone- androstanediol dihydrotestosterone (Figure 1). This pathway is believed to be involved in normal masculinization during physiological development and abnormal virilization in pathological conditions.[16] Furthermore, it may mediate the androgen dependent responses in individuals who have low plasma T levels.[17]

Low plasma T levels are correlated with reduced libido and erectile dysfunction. In a study of 434 males conducted by Zitzmann et al., it was shown that the symptoms of hypogonadism was inversely correlated with the plasma T levels and the biochemical testosterone thresholds of serum testosteron were 430 ng/dL and 230 ng/dL for libido reduction and erectile dysfunction respectively.[18] On the other hand preserved erectile functions in some men in spite of low androgen levels, may be explained by androgen polymorphism. Androgen dependent-tissues exhibit varying sensitivity to circulating T levels. Moreover, testosteron is not the only androgen influencing erectile function which is also effected by DHT, dehydroepiandrosterone (DHEA), DHEA sulfate and estrogens.[19]

Sexual Cycle

The first model of sexual cycle was the EPOR model described by Master and Johnson in 1966.[20] This model was defined as a four-phase model, including excitement, plateau, orgasm/ejaculation and resolution phases.

The Effects of Testosterone on Sexual Functions

Libido:

T, DHT, prolactin, estrogen, cortisol, dopamine, oxytocin, norepinephrine, melanocortin, serotonin are the hormones and neurotransmitters that influence libido. Libido is the result of the positive interactions between internal cognitive factors (fantasy, imagination), neurophysiological mechanisms and emotional components.[21] The areas of the brain involving sexual impulse and libido are; amygdala, medial pre-optic area (MPOA), paraventricular nucleus of hypothalamus, frontal and prefrontal areas, periaqueductal gray body, cingulate gyrus (Brodman area 24 B24) and these areas contain abundant androgen receptors.[12,22]

The sexual behavior in humans is multifactorial and although its biological basis is still unknown, the hormonal route has been proven to play a significant role.[23,24] Testosteron was shown to control dopamine release in the MPOA by increasing nitric oxide (NO) synthesis in rats.[25] In the studies among hypogonadal patients, sex drive was increased following testosterone replacement therapy (TRT) and furthermore, in a study conducted by Corona et al., decreased sex drive was observed in parallel with the plasma testosteron level reduction.[24,26,27]

In the analysis of the hormones influencing libido, other than T; although prev ious studies demonstrated the association of low libido with decreased level of DHT in patients on 5 alpha reductase inhibitors, the effect of DHT on sexual functions is still controversial.[28] Prolactin; hyperprolactinemia generally has a suppressive effect on libido.[22,29]

Estrogen; the sexual functions were not altered by the use of tamoxifen or testolactone in males with normal plasma T levels.[30] However an improvement of libido was observed during transdermal estradiol therapy in some patients with aromatase deficiency.[31] In an multi-center study of 3400 patients, conducted by European Male Aging Study, no relationship was found between estradiol and sexual functions in middle-aged and elderly (40-80 years) males.[32]

Erection:
Psychogenic, reflexogenic and nocturnal are the three types of erection. Psychogenic erection was observed in 25% of the 16 patients following castration and reflexogenic erection occurs via cavernous nerve. Free T levels of the patients with psychogenic erection were reported to be more than 112.5 ng/dl.[33] Reflex erections disappear if the pudendal and cavernous nerves are damaged whereas they are preserved in patients with upper spinal cord damage. Nocturnal erections occur during the REM phase of sleep. Plasma T values below 200 ng/dL have been shown to have a tendency to decrease the number of nocturnal erections.[34] The relationship between different types of erection and testosterone levels is shown in the Table 1.

The effects of testosteron on the erection are observed in both central and peripheral pathways.

Central effects

Dopamine, oxytocin, norepinephrine and serotonin are the influential neurotransmitters in the coordination of the central domain of the physiology of the erection. Particularly dopamine plays a key role in the sexual functions. T was also shown to control dopamine release by increasing NO synthesis.[25] Furthermore, erectile response elicited by the electrical stimulation of the MPOA was found to be significantly diminished in the castrated rats and the response was improved by T replacement.[17,35]

Peripheral

The major effect of T is on the parasympathetic postganlionic neurons.[36] Their structure includes neuronal nitric oxide synthases (nNOS) and the NO/cGMP pathway which is of critical importance for erectile function. The decrease in erectile response to the electrical stimulation of the cavernous nerve in the castrated adult rats is related to the declined neural activity and nNOS in penis; both changes may be prevented by the administration of androgens.[37-39] Armagan et al. and Rogers et al. reported that ultrastructural changes were observed in the dorsal nerve after castration and these were ameliorated by TRT.[40,41]

Smooth muscle

Penile smooth muscle tone plays an important role in the hemodynamic events necessary for penile erection and relaxation. The previous animal studies demonstrated that castration led to the impairment of the balance between the trabecular smooth muscle

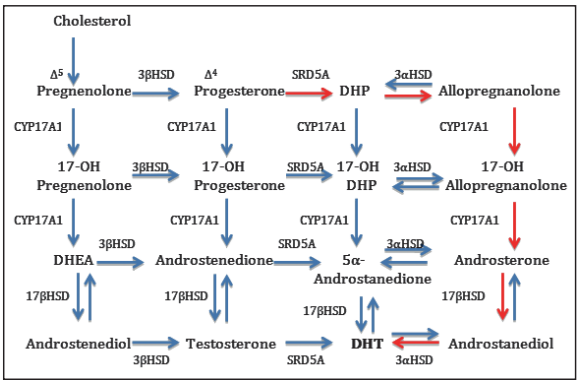

Figure 1: Alternative backdoor pathway for DHT biosynthesis (⟶). **3βHSD:** 3β hydroxysteroid dehydrogenase, **SRD5A:** 5α-reductase, **3αHSD:** 3α-hydroxysteroid dehydrogenase, **CYP17A1:** 17α-hydroxylase, 17/20 lyase, **17βHSD:** 17β-hydroxysteroid dehydrogenase, **DHP:** dihydroprogesterone.

and connective tissue; apoptosis and the matrix of extracellular connective tissue escalated and thus imparing erectile functions. The alterations in the tissues and functions of the castrated animal were improved after the androgen replacement therapy.[42]

Accumulation of adipocytes was observed in the subtunical area of the cavernous body after orchiectomy in rabbits and it was resolved by T replacement. These tissue changes are believed to be related to the diminished intracavernosal pressure response to the pelvic nerve stimulation and they may lead to a veno-occlusive dysfunction.[43]

Endothelium

Endothelium modulate the vascular tone and erectile physiology via autocrin, paracrine and endocrine mechanisms. It is known that T deficiency may lead to endothelial damage and the endothelial damage is restored by T replacement.[44,45] In the recent studies, it is demonstrated that androgens stimulate the proliferation of the endothelial progenitor cells which are important for the repair of endothelial damage.[46] Androgens increase the synthesis and release of NO in the endothelium. Androgen deficiency leads to a decrease in eNOS activity and endothelial cell growth, release of inflammatory cytokines, dysregulation of the fibrinolytic factors and finally an increase in vascular tone and permeability.[47]

Ejaculation

Testosterone has effects on all stages of ejaculation, both central and peripheral. It was shown that androgen receptors were expressed in all supraspinal sites controlling ejaculation. Additionally, the spinal nucleus of the bulbocavernosus, an important area for controlling ejaculation was demonstrated to be androgen dependent.[48,49] Testosterone changes the

Table 1. Erection types and T values	
Psychogenic Erection	Free T 112.5 ng/dl
Reflexogenic Erection	T threshold value 50 ng/dl
Nocturnal Erection	T threshold value 200 ng/dl

expression of the gastrin releasing peptide in the lower spinal cord mediating the ejaculation reflex.[50] Also other muscles controlling ejaculation, the bulbocavernous, ischiocavernous and levator ani muscles are also androgen dependent.

Furthermore, the ejaculate volume was found to be reduced in people receiving ADT.[51] In a study conducted by Corona et al., among the men aged between 25-39 years, plasma total testosterone and free testosterone levels were reported to be higher in men presenting with premature ejaculation, in comparison to the patients with delayed ejaculation or normal ejaculation time. In addition these hormones were demonstrated to be lower in patients with delayed ejaculation and aged between 55-70 years. According to these results, T plays a facilitator role in the control of the ejaculatory reflex.[52]

Androgen Deprivation Therapy (ADT)

Since the demonstration of Huggins and Hodges that orchiectomy and estrogen may be beneficial in the treatment of the patients with metastatic prostate cancer in 1941, androgen deprivation therapy has been seen as a primary treatment modality in advanced prostate cancer.[6,53]

Nowadays the treatment options include; (Table 2)

1)Surgical castration: Bilateral orchiectomy, may provide the castrated levels of testosterone <50 ng/dL in a period of time less than 12 hours.

2)Estrogens: LHRH released from hypothalamus suppresses Leydig cell functions. Estrogens have an inactivation effect on androgens and cytotoxic effects on prostate epithelium, in vitro. Diethylstilbesterol is the most commonly used estrogen and a daily dose of 5 mg is associated with a high incidence of cardiovascular toxicity. Although diethylstilbesterol has therapeutic efficacy at a daily dose of 1 mg, it has higher rate of cardiovascular side effects in comparison to bilateral orchiectomy.

3)LHRH agonists: They have been in use for more than 15 years and is still the most widely used agent.[54] Initially, they lead to a transient increase in the LH and FSH and thus induce T production, called "flare up phenomenon" by stimulating pituitary LHRH receptors. Later on, in the presence of the non-pulsatile chronic LHRH administration, FSH and LH production is suppressed and T levels decrease to the castrate levels within 2 to 4 weeks.

4)LHRH antagonists: They bind immediately and competitively to the pituitary LHRH receptors. Their effects start within 2 days. A rapid fall is observed in the plasma FSH, LH and T levels and they do not cause the flare phenomenon.

5)Antiandrogens: Antiandrogens compete with testosterone and DHT for androgen receptors and competitively block the androgen receptors. Consequently, they induce apoptosis and prevent cancer growth. Based on their chemical structure, antiandrogens are divided into two groups; 1) steroidal and 2) nonsteroidal. While nonsteroidal antiandrogens exhibit their effects only by exerting competitive inhibition, steroidal antiandrogens inhibits also the pituitary gland and exert progestational effects. Therefore steroidal antiandrogens diminish T levels. Nonsteroidal antiandrogens do not effect the LH and T levels.

6)Adrenal Ablation Agents:
Ketoconazole: Ketoconazole is an antifungal agent that inhibits cytochrome P450 and it is used at a dose of 400 mg three times daily. Although ketoconazole is a rapid acting agent, plasma testosterone levels return to normal in 5 months in case it is given as monotherapy.[55] Consequently, ketoconazole is preferred in castration-resistant prostate cancer.

Abiraterone acetate: Abiraterone acetate is developed from ketoconazole and it is an inhibitor of CYP17. Abiraterone acetate reduces intracellular T level by inhibiting T synthesis at the adrenal level. It is used in castration-resistant prostate cancer.[56]

The effects of ADT on sexual functions

In 1941 Huggins et. al. reported that all cases experienced loss of sex drive and erectile dysfunction after castration.[6] In a study of 44 patients receiving combined androgen blockade, libido loss was observed in 70% of the patients whereas erection was preserved in 25% of the patients who had a normal erectile function before the treatment. However it should be mentioned that the erections were not fully rigid.[7] In a study, Greenstein evaluated 16 patients who were sexually active before castration and determined that libido was significantly decreased in all patients after the castration and they already started to experience some degree of erectile dysfunction. Penis circumference and the quality

Table 2. Androgen deprivation therapy treatment options			
Drug Class	**Drugs**	**Site of Aciton**	**Mechanism of Action**
LHRH agonists	Leuprolide Goserelin	Anterior Pituitary Gland	Decreases release of LH through down-regulation of GnRH receptors
LHRH antagonists	Abarelix Degarelix	Anterior Pituitary Gland	Directly inhibits GnRH receptors
Adrenal Ablating Drugs	Ketoconazole	Adrenal Gland	Decreases androgen synthesis from steroid precursors through inhibition of cytochrome P450 enzymes
Antiandrogens	Flutamide Bicalutamide Nilutamide	Prostate Gland	Inhibits androgen receptor ligand- binding domain through competitive binding

of erection were assessed during visual stimulation, erotic movie, and functional erection was observed in 4 patients (25%).[33] Potosky et al, compared the 132 patients who only underwent orchiectomy within 1 year after the diagnosis of prostate cancer to the 299 patients receiving a GnRH agonist in terms of sexual function. While libido loss was raised by a rate of 36% in the orchiectomy group, it remained 26% in the GnRH agonists group. On the other hand while the rate of erection loss increased from 35% to 79% in the orchiectomy group and it increased from 38% to 73% in the GnRH agonists group. No significant difference was observed between the ADT types.[57] Marumo et al., evaluated T levels, erectile functions and nocturnal penile tumescence (NPT) in nine sexually active patients with prostate cancer after the administration of GnRH agonist. Complete libido loss and lack of sexual activity as well as significant reduction of NPT number ($p<0.01$) were observed in the patients when the T levels were suppressed to the castrate levels.[58] In a study conducted by Green et al., 62 patients with non localized prostate cancer were assigned into 5 groups including; 19 patients receiving goserelin, 18 patients receiving leuprorelin, 11 patients receiving cyproterone acetate, 14 patients under close surviallence and 15 control patients and different treatment options were assessed. Sexual functions were significantly decreased in the groups receiving goserelin, leuprorelin and cyproterone acetate but no significant difference was not detected in the monitored and control groups (Table 3).[59]

Although loss of orgasm and ejaculation among the patients on ADT have been reported in many studies, there are limited data in the background of evidence based medicine. On the contrary, in a case presentation, Warkentin et al reported the presence of orgasm in a patient on ADT.[60] According to the hypothesis of Mulhall et al. the adverse effects of hormone ablation therapy on the sexual behavior differ in proportion to different threshold values of testosterone.[61]

Furthermore, even the diagnosis of cancer may exert negative impacts on the sexual functions before the treatment. A study was conducted on this issue and in the assessment of 158 prostate cancer patients who were waiting for the treatment, decreased sexual activity was detected in 20% of the patients and libido loss was detected in 15% of the patients.[62]

Moreover, sexual dysfunction is common among the partners of the patients who are on ADT due to prostate cancer. The rate of the decline in sexual intercourse was found as 33% in the partners of the patients who are on ADT.[63]

Treatment:

Treatment alternatives include; intermittent androgen deprivation therapy (IADT), PDE5 inhibitors, vacuum erection devices, intracavernosal injection therapy, penile prosthesis implantations, estrogen administration, and sexual counseling before and after the treatment.

IADT was demonstrated to be associated with a significantly lesser sexual adverse effects in many studies. In a recent study, the 314 and 312 patients on intermittent and continuous androgen deprivation therapy respectively were randomized into two groups. Approximately 15 months later, sexual activity was preserved in 28% and 10% of the patients who received the former and latter therapies.[64] 173 patients were randomized [IADT:86, Continuous androgen deprivation therapy (CADT):83] by Nicolas Mottet et al. in a study and they also reported that libido and erectile functions were significantly better in the IADT group.[65]

DiBlasio et al. conducted a study on sexual and erectile dysfunctions among 395 patients on ADT and demonstrated that 27 (47%) patients benefited from the treatment. 18 patients benefited from PDE5 inhibitors, 2 patients benefited from PgE-1 analogues, 2 patients benefited from the vacuum erection device, 1 patient benefited from penile prosthesis and 4 patients benefited from combination therapy.[66] In this study, the efficacy rate of PDE5 inhibitors was reported as 50%. The low efficacy rate may be related to decreased plasma T levels. In addition the NOS, testosterone is also important for PDE5 expression.[67] Significant increase in the response rates of PDE5 refractory hypogonadal men, testosterone less than

Table 3: Sexual functions in patients on ADT

Study	N	Libido	ED
Rousseau et al.[10]	44 (CAB)	A decline of 70 %	56% Before the treatment and 19% after the treatment
Greenstein et al.[33]	16 (LHRH analogue or surgical castration)	A strong libido in all patients before the treatment (mean score:5), a decline in libido after the treatment (mean score:1.8).	ED in all patients
Marumo et al.[58]	9 (LHRH analogue)	Libido loss in all patients	ED in all patients
Potosky et al.[57]	132 (orchiectomized)	Libido loss was increased from 28% to 64%.	From 35% to 79%
	299 (LHRH agonist)	Libido loss was increased from 32% to 58%.	From 38 % to 73%
Deborah P et al.[78]	67 (ADT)	Health-related quality of life (HRQOL) Sexual function Before ADT 24.9 After ADT 14.7	Health-related quality of life (HRQOL) Sexual function Before ADT 24.9 After ADT 14.7
Green HJ et al.[59]	37 (LHRH analogue)		Sexual functions Goserelin ($p < 0.001$), leuprorelin ($p = 0.033$)
	11 (CPA)		CPA ($p = 0.067$) A significant decline in comparison to the control and non-treatment groups
Basaria S et al.[79]	20 (LHRH analogue)	Watt's Sexual Func tion Questionnaire score Libido ADT group:10.7 non ADT group:19.4 control:20.9 ($p<0.001$)	It is more difficult to get and maintain the erection in comparison to the other groups
Ng E et al.[80]	250 (CAB)	Libido was present in 63% of 111 patients (strong libido in 28%) before the treatment. The rate of strong libido decreased to 9.6% after the treatment.	43% of 97 patients had no ED before the treatment. This rate decreased to 15% after the treatment.

400 ng/dL, after testosterone replacement supported this hypothesis.[68,69]

In both animal and human studies, estrogen efficacy has been reported in preserving and even increasing libido in patients on ADT.[70-72] Estrogen receptors were found in the MPOA, medial amygdala and the nucleus of the stria terminalis which are important for sexual behavior.[73] The mechanism of estrogen on libido increase has not been elucidated. It was shown that estrogen might have effects on the peripheral tissues connected with orgasm, on the genital area sensitivity and pelvic floor muscles in particular.[74,75]

In addition, 5-hydroxytryptamine (5-HT) is believed to be an inhibitor neurotransmitter under the control of sex drive and the administration of buspirone, which is a 5-HT inhibitor, was reported to increase libido in the patients.[76,77]

CONCLUSION

ADT is the main treatment for advanced or metastatic prostate cancer. ADT administration has a negative impact on the sexual function and thus impairs the life quality of both the patient and his partner. Androgens play an essential role in the central and peripheral domains of the erectile tissues and other sexual structures. However androgens alone are not sufficient to explain the impairment in the sex life .

Complex biochemical interactions were demonstrated in the hormonal control of sexual behavior and the pathophysiology keeps its mystery. The treatment options include PDE5 inhibitors, vacuum devices, intracavernosal injection therapy, penile prosthesis, and sexual counseling.

* The authors declare that there are no conflicts of interest.

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