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REVIEW

Impact of androgen deprivation therapy on sexual function

Clarisse R Mazzola and John P Mulhall

Many patients with prostate cancer for whom androgen deprivation therapy (ADT) is indicated are young and desire to remain sexually active. In such patients, the side effects of androgen therapy on sexual function can be a source of serious reduction in overall quality of life. Providing the appropriate treatment options in this patient population is therefore essential. Nevertheless, treating such patients is challenging and an understanding of the underlying mechanisms of sexual physiology and pathophysiology is crucial to optimal patient care. In this paper, we reviewed what was known regarding the effects of ADT on sexual function in animal models and we also provided a detailed review on the effects of ADT on sexual health in humans and its treatment.
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INTRODUCTION

Since the introduction of the concept of hormonal dependence of prostate cancer in 1941 by Huggins and Hodges,[1] a variety of approaches to achieving androgen deprivation have been utilized: bilateral orchiectomy, use of estrogenic compounds (diethylstilbestrol, oestradiol and polyestradiol phosphate), and more recently, medical castration in two forms: luteinizing hormone-releasing hormone (LHRH) analogues such as leuprolide, goserelin, triptorelin and histrelin, and androgen blockade with anti-androgens such as flutamide, bicalutamide and nilutamide.

LHRH agonists reduce testosterone to castrate levels by suppressing the production of androgens by the testes, which represent 90%–95% of the total androgen production, with the remaining 5%–10% being produced by the adrenal glands. LHRH agonists have no effect on the production of androgens by the adrenal glands contrary to anti-androgens, which block the effects of adrenal androgens at the level of the androgen receptors. Several inhibitors of adrenal androgen production are also used as second-line hormone therapy, such as ketoconazole, corticosteroids and aminoglutethimide.

Regarding the use of androgen deprivation therapy (ADT), it is indicated for first-line treatment for symptomatic metastatic prostate cancer,[2] and as neoadjuvant therapy prior to radiotherapy.[3,4] In its most common use, ADT is also prescribed as a treatment for patients with biochemical recurrence after first-line treatment, or who present locally advanced disease, lymph node metastasis or metastatic disease.

Many aspects of ADT, however, remain unsolved such as, for example, what represents the best time for ADT to be administered, what is the best regimen for administration, continuous or intermittent therapy, and what are the benefits of either maximal androgen blockade (combination of LHRH agonists and anti-androgens); or anti-androgens alone or combined with 5α-reductase inhibitor therapy. Another significant issue is how to optimally manage the adverse effects of ADT.

Many patients with prostate cancer for whom ADT is indicated are sexually active and wish to continue to be so after treatment. Loss of libido and erectile dysfunction (ED) are well-known side effects of this treatment and are usually attributed to the decrease in testosterone levels. Recent animal studies have demonstrated that the underlying mechanisms by which the ADT affects sexual function are complex and suggest that the hormonal control of sexual behavior may be mediated through more than one pathway.

As shown previously by Mulhall *et al.*,[5] erectile function is essential for quality of life, overall self-esteem and overall relationships. However, this requires a thorough understanding of the underlying physiology of sexual function. In this paper, we reviewed what was known in the scientific literature regarding the side effects of ADT on sexual function, and we discussed the most efficient treatment options at the time of those effects.

PHYSIOLOGICAL ROLE OF ANDROGENS IN SEXUAL BEHAVIOR—ANIMAL STUDIES

The studies presented in the literature have mainly used bilateral orchiectomy as a model, which may not, at first sight, lead to the exact same consequences as chemical androgen deprivation using LHRH agonists or anti-androgens as used in humans. Furthermore, in contrast to what is seen in humans, rodents' adrenal cortex does not synthesize androgens. Thus, animals have no peripheral source of circulating androgen precursors and after bilateral orchiectomy, are totally devoid of any androgens.[6]

The animal studies in the literature studied mainly three variables: mount, intromission and ejaculation and their link with hormonal assays or biological measurements. Therefore, those models do not allow

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the study of loss of libido or orgasm that are more specific to humans, and that can in turn affect sexual satisfaction. Despite these limitations, animal studies have shown that accomplishment of sexuality in males is a complex phenomenon. As those hormones act through the interplay of neurological and endocrine factors both at the central and peripheral level, we will divide our discussion accordingly.

CENTRAL ACTIONS OF ADT ON MALE SEXUAL BEHAVIOR

Effect on the medial preoptic area

The central control of sexual activity is dependent on the levels of dopamine in the medial preoptic area (MPOA). In a study by Sato *et al.*,[7] the regulation of dopamine levels through the nitric oxide–cGMP pathway played a facilitative role in male rat copulation. In a study by Yeh *et al.*,[8] administration of *Gingko Biloba* extract (EGb 761) to male rats increased the number of intromissions and was associated with higher levels of dopamine in the MPOA, but had no effect on the number of mounts, mount latency, intromission latency, ejaculation latency or post-ejaculatory interval, and seemed to be related to the activity of not all but a subregion of MPOA. In another study by Suzuki *et al.*,[9] including 24 castrated male rats, erectile responses elicited by electrical stimulation of the MPOA were eliminated following castration, but restored after testosterone replacement. This illustrates the crucial role of testosterone in the central pathways that oversee sexual function.

Effect on lumbar spinal cord

Studies performed by Sakamoto *et al.*[10,11] showed that the lumbar spinal cord contained local neural circuits at the L3–4 levels that were important in regulating male sexual behaviors through the release of gastrin-releasing peptide (GRP) at the lower lumbar spinal cord (L5–S1 level). This peptide is a member of the bombesin-like peptide family. It is predominant in male lumbar spinal cord and vestigial in females.[12,13] In another study by Sakamoto *et al.*,[11] the urogenital development of genetically XY rats mutated with a dysfunctional androgen receptor gene was shown to be a female system, showing the androgen-dependent nature of the GRP gene. The same authors showed the pharmacological stimulation of GRP receptors with GRP agonists allowed the restoration of penile reflexes and ejaculation after castration in male rats.[14] Conversely, the same authors showed that the inhibition of GRP receptors was able to significantly attenuate penile reflexes and ejaculation rate in normal male rats.[14] These recent data provided substantial insight into another way by which ADT might affect male sexual function, through the dysregulation of the GRP pathway.

PERIPHERAL ACTION OF ADT ON MALE SEXUAL BEHAVIOR

Effects of androgens on external genital organs

Androgens play a neurotrophic role on the penile dorsal and cavernous nerves. In a study by Armagan *et al.*,[15] 2 weeks after castration, male rats started to show ultrastructural alterations of their penile dorsal nerve compared to control rats. These alterations included signs of nerve degeneration, and especially myelin sheath degeneration. In a study by Suzuki *et al.*,[9] the same effect of castration was shown to affect cavernous nerves as well. Indeed, in their study, performed on 24 male rats, intracavernosal pressure elicited with electrical stimulation of the cavernous nerve was shown to be significantly lower in castrated male rats compared to the intact controls 0.31 (0.22–0.39) median intracavernosal pressure/blood pressure ratio compared to 0.58 (0.40–0.68) ($P<0.01$, Mann–Whitney test). Moreover, when testosterone replacement was administered, it was shown to restore erectile function. Thus, testosterone seems to play a neuroprotective role on the peripheral neurological structures that are essential for normal male sexual behavior. These data suggest that ADT may lead to structural neural alterations which may be implicated in sexual dysfunction in this population.

Androgens maintain penile trabecular smooth muscle structure. ADT has a direct effect in altering penile smooth muscle structure, in decreasing the levels of circulating androgens that are known to play a physiological role in maintaining the integrity of both smooth muscle, and are capable of promoting smooth muscle cell growth.[6]

ADT also indirectly impacts penile smooth muscle structures through the decrease of penile erection. Indeed, in the absence of erection due to ADT, cavernosal oxygenation is diminished and therefore, smooth muscle cells are exposed to a prolonged hypoxic environment.[16] This leads to the inhibition of prostaglandin E1, interfering with its natural inhibiting effect on profibrotic substances, such as transforming growth factor-β1 and transforming growth factor-β1-dependent endothelin-1.[17,18] Consequently, TGF-β1 is permitted to promote connective tissue synthesis (especially collagen I and III), with the subsequent replacement of trabecular smooth muscle.[17,18] In a study performed on rats, androgen deprivation by surgical or medical castration resulted in reduction in smooth muscle content and structural alterations in the corpus cavernosum leading to venous leak.[19] Castrated dogs have also been shown to have significantly higher cavernosal collagen/smooth muscle ratios.[20] A decrease in smooth muscle/collagen ratios in the corpora cavernosal leads to the development of venous leak.[21]

Androgens maintain endothelial structure and function. Androgens play a role in maintaining endothelial structure and function in many ways.

First of all, androgens have been shown to be involved in the differentiation of pluripotent progenitor vascular stroma cells.

Secondly, there is a body of evidence supporting the role of testosterone in the response to endogenous vasodilators.[22] Indeed, testosterone was shown to upregulate the expression and activity of nitric oxide synthase isoforms in the corpus cavernosum.[23–28] And in castrated animals, testosterone or 5α-dihydrotestosterone (DHT) administration was shown to be able to restore the erectile response and nitric oxide synthase expression in the penis.[23–28] The expression and activity of phosphodiesterase type 5 were shown to be under the control of androgens as well.[29–31] This enzyme hydrolyzes cGMP in vascular and trabecular smooth muscle into GMP, leading to smooth muscle relaxation and thus penile flaccidity. In some studies performed in rats and rabbits, this enzyme was shown to be reduced by castration but restored by androgen supplementation.[29–31]

Thirdly, androgens indirectly maintain endothelial function through the prevention of fibrosis. During erection, smooth muscle expands in a three-dimensional fashion under NO control, and induces the compression of the subtunical venules located externally between the tunica albuginea and the corporal smooth muscle. After ADT, collagen deposition causes the muscle to fail to expand adequately, subsequently leaving subtunical venules in a non-compressed state, leading to venous leak. In a study by Nehra *et al.*,[21] in human corporal tissue biopsy specimens taken at the time of cavernosometry, venous leak was found to occur when the smooth muscle content in the penis dropped below 40%. And the lower this figure (below 40%), the greater the magnitude of the leak.[21]

Different androgens impact male sexual behavior

In castrate animal studies, testosterone was shown to be able to restore male sexual behavior, while DHT could not when administered

alone.[32–34] However, DHT and testosterone administered together restored sexual behavior to precastration levels more rapidly than did testosterone alone[33] in a study performed on castrated hamsters (more rapid recovery of ejaculatory behavior, shorter ejaculation latencies and a greater number of ejaculations in 30-min tests). In another study by Arteaga-Silva *et al.*,[32] androstenedione was shown to be more potent than testosterone in restoring male sexual behavior, ejaculatory behavior being displayed by most castrated subjects with a lower dose of androstenedione than of testosterone, and long intromissions being shown by all androstenedione-treated hamsters but only 20% of testosterone-treated ones. Nevertheless, in the same study, DHT was shown to be the one of the androgens with the highest potency to stimulate penile epithelium growth due to its higher peripheral androgenic potency. As well, recent studies[35–39] have established that paradoxical sleep deprivation (PSD) and cocaine administration induced genital reflexes (penile erection and ejaculation) in adult and old rats. However, in those studies, testosterone levels were lower in the PSD arms than in the control, while progesterone and corticosterone levels were increased. The authors have suggested that the interaction of PSD and cocaine probably enhances dopaminergic transmission in the brain and may thus potentialize genital reflexes in male rats. Nevertheless, in other studies, increase in penile erections seemed to be mediated by progesterone. Indeed, when progesterone blockade with mifepristone was accomplished in male rats submitted to sleep deprivation and cocaine, it was found to induce a significant decrease in penile erection.[40] In contrast, when progesterone was administered, penile erection was shown to be significantly increased.[37] This suggests that progesterone has an effect on erectile responses. As suggested by the significant decrease observed in the duration of sleep deprivation episodes in male rats under mifepristone, it could be postulated that progesterone exerts a central effect. A peripheral effect of progesterone is also suggested by a study by Auchus,[41] in which a 'backdoor pathway' was also shown to exist allowing a peripheral conversion of progesterone to 5α-DHT without formation of testosterone. This would explain how some androgen-dependent responses could persist in humans in spite of low serum testosterone levels. As highlighted by those studies, little is known at the moment on the hormonal control of male sexual behavior except that it involves a complex series of biochemical interactions, and the exacts consequences and effects of ADT remain thus unclear.

EFFECT OF THE ENVIRONMENT ON THE ENDOCRINE CONTROL OF MALE SEXUAL BEHAVIOR

Normal male sexual activity seems to be dependent on a very precise and complex hormonal milieu that is not currently fully understood. In some animals as well, there seems to be an influence of seasonal variation in reproductive activity.[42] Nevertheless, this equilibrium is fragile and some studies have shown that the environment can also impact on it. Indeed, some stressors such as food restriction,[43–45] sleep deprivation[35–39] and exposure to the radiofrequency emitted by a conventional mobile phone[46,47] have been shown to be able to cause a stress sufficient enough to disturb it.

More interestingly, a study by Andersen *et al.*[48] added that different stressors resulted in different steroid responses. Indeed, in their study, various levels of testosterone, progesterone, corticosterone, estradiol and estrone were found in five groups of 10 rats, following the assignment of each group to a different stressor (PSD, restraint, electrical foot shock, cold and forced swimming). Thus, ADT could both alter the fragile equilibrium of male sexual activity and also lead to the disappearance of steroid response to stressors.

EFFECTS OF ADT IN MEN

Sexual activity

The effects of ADT on sexual activity, taken in its entirety, have been studied. One must be noted, however, that sexual activity is a very non-specific primary outcome measure that can be affected by a large variety of sexual dysfunctions (ED, decreased libido, *etc.*).

Potosky *et al.*[49] in a prospective cohort of 431 men, showed that the percentage of men who were sexually inactive increased from 48% to 83% after orchiectomy and from 45% to 80% after gonadotropin-releasing hormone agonist administration. Marumo *et al.*[50] observed in nine sexually active prostate cancer patients who underwent ADT with 3.75 mg of leuprorelin acetate every 4 weeks as monotherapy, that a reduction in serum testosterone concentrations to levels inferior to 10 ng dl^{-1} at 12 weeks, preceded total suppression of sexual activity (no intercourse for 12 weeks during treatment) in all patients. Nevertheless, in another study by Jannini *et al.*,[51] performed on 83 patients with ED compared to 30 age-matched control patients, reduced total and free testosterone levels were seen in the former group (11 ± 2 nmol l^{-1} *vs.* 18 ± 5.5 nmol l^{-1} total testosterone and 56 ± 23 pmol l^{-1} *vs.* 79 ± 27 pmol l^{-1} free testosterone, respectively) (both $P<0.001$). A significant increase in serum total and free testosterone levels (16 ± 4 nmol l^{-1} and 74 ± 22.5 pmol l^{-1}, respectively) was observed in those patients who achieved normal sexual activity 3 months after commencing ED therapy ($P<0.001$), while serum testosterone levels did not change in patients to whom ED therapies were ineffective. There seems thus to be a vicious circle in which the decreased sexual activity subsequent to lowering testosterone, causes in turn free and total testosterone levels to fall further.

Nocturnal erections

In a study performed by Hirshkowitz *et al.*,[52] 10 healthy young men were administered LHRH agonists or placebo for a 12-week period, subjects of the ADT group had significantly worse nocturnal erection rigidity and tumescence compared to the eugonadal control group. Those results were in keeping with previous results from Carani *et al.*[53] In the study by Marumo *et al.*,[50] a significant reduction in the frequency, magnitude, duration and rigidity of nocturnal penile tumescence was observed in leuprorelin acetate treated prostate cancer patients on Rigiscan monitoring units. This outcome was shown to be subsequent to the reduction in serum testosterone concentrations. In this study, the number of nocturnal penile erections decreased from 0.43 per hour prior to treatment to 0.03 per hour 12 weeks after initiation of therapy ($P<0.01$).

In a study by Martinez-Jabaloyas *et al.*,[54] in 165 men with ED who were screened for total and free testosterone levels, 5% and 18% were found to be hypogonadal when analyzing total and free testosterone levels, respectively. On multivariate analysis, only lower free testosterone levels were associated with absence of nocturnal erections. This was in keeping with the results from a previous study performed by Ahn *et al.*,[55] on a cohort of 213 patients with lower urinary tract symptoms aged 31–78 years, and who had no confirmed ED and who were evaluated using the International Index of Erectile Function (IIEF) questionnaire. In this cohort, regression analysis showed that free testosterone level was modestly correlated with the erectile function domain of the IIEF ($r=0.2136$, $P=0.005$). Some authors nevertheless stress that the testosterone threshold value below which sexual behavior is affected might well vary significantly from one individual to another.[53,54,56,57]

In a study by Foresta *et al.*[58] performed on 40 healthy men over 60 years of age, a significant decrease in frequency, duration and degree of

nocturnal erectile episodes was observed compared to a matched group of 30 young volunteers aged 26–40 years old. This decrease was more marked in patients with low serum testosterone levels. In this subgroup of patients, DHT treatment significantly improved nocturnal penile tumescence parameters without reaching those of the controls ($P<0.001$).

ED

The role of androgens in sustaining erectile function in men is well illustrated by studies performed on hypogonadal men. Indeed, hypogonadism was shown to be associated with a decline in erectile function and in the erectile function domain scores on the IIEF.[6,59,60] In a study performed by Kratzik *et al.*[60] on 675 workers aged from 45–60 years, screened for their erectile function and serum testosterone levels, severe cases of ED (IIEF-5 score 7 or less) were significantly associated with a decrease in total testosterone and bioavailable testosterone (BAT). Individuals with low bioavailable testosterone ($\leqslant 1$ ng ml^{-1}) had a three times higher risk of severe ED compared with men with BAT greater than 1 ng ml^{-1} (odds ratio: 3.045, 95% CI: 1.088−8.522, $P=0.034$), even after adjustment for age and body mass index. Conversely, androgen supplementation was shown to improve erectile function in hypogonadal men.[59]

The consequences of ADT on erectile function have been observed in men.[61] In a study by Potters *et al.*,[62] studying the erectile function outcomes of 482 potent prostate cancer patients before treatment, the 5-year actuarial potency of brachytherapy patients, defined as the ability to achieve erection sufficient for penetration during intercourse without medications or devices, was significantly worse when neoadjuvant androgen deprivation had been given (76% *vs.* 52%). In this study, Cox regression analysis showed that pre-treatment use of neoadjuvant ADT was a predictor of ED ($P=0.0001$).[62] In another study by Mazzola and Mulhall,[63] the erectile function outcomes of 38 patients who had received neoadjuvant ADT prior to radical prostatectomy were compared to those of a contemporary matched cohort of 94 patients treated with radical prostatectomy alone. In this study, the incidence of venous leak 6 months after surgery was 60% in the ADT group compared to 20% in the control group ($P<0.001$). Likewise, the proportion of men with an erectile function domain score $\geqslant 24$ at 18 months after surgery was 22% in the ADT group compared to 50% in the control group ($P<0.01$), even when controlled for nerve sparing status (**Table 1**).

In a study[49] performed by the Prostate Cancer Outcomes Study of the Surveillance, Epidemiology and End Results program, it was shown that 69% of the men who were potent before ADT treatment lost their potency after treatment. There did not seem to be any statistical differences in terms of ED in between the types of ADT therapy. In a later study[64] by the same group, 86% of men undergoing ADT subsequently experienced ED, compared to 58% of radical prostatectomy patients, 43% of radiotherapy patients and 33% patients undergoing watchful waiting ($P<0.0001$). In another study by Potosky *et al.*,[65] the erectile function outcomes of a cohort of 88 ADT patients were compared to a matched group of 223 prostate cancer patients receiving no treatment. In this study, 80% of those on ADT reported being impotent after 1 year compared with 30% of those receiving no treatment ($P<0.001$).

To counterbalance these conclusions, it is not infrequent to observe that erection is preserved in some men with low androgen levels. As suggested by Hatzimouratidis *et al.*,[59] the androgen receptor polymorphism might explain varying inter-individual sensitivities to circulating testosterone levels. Each androgen dependent tissues might as well have various sensitivities to different circulating testosterone levels.[59] Some authors have suggested that the testosterone threshold value below which erectile function is affected is about 10% of the normal range of testosterone and that below this threshold value, erectile function would be affected in a dose-dependent fashion.[59,66] Some have suggested that it is free testosterone and not total testosterone that is associated with erectile function.[54,55,67,68] As highlighted by

Table 1 Human data linking androgen deprivation therapy to ED

Authors	*Year*	*Study population*	*Results*
Mazzola *et al.*[63]	2011	38 NAAD+RP patients 94 patients with RP alone	Incidence of CVOD 6 months after surgery: 60% in NAAD+RP *vs.* 20% in the RP alone patients ($P<0.001$) IIEF $\geqslant 24$, 18 months after surgery: 22% in the NAAD+RP group *vs.* 50% in the RP alone patients ($P<0.01$)
Kratzik *et al.*[60]	2005	675 men aged 45–60 years	Severe cases of ED (IIEF-5 score 7 or less) significantly associated with a decrease in T and BAT Individuals with low BAT (1 ng ml^{-1} or less): three times higher risk of severe ED compared with men with BAT greater than 1 ng ml^{-1} (odds ratio: 3.045, 95% CI: 1.088–8.522, $P=0.034$)
Hoffman *et al.*[64]	2003	2365 patients with localized CaP	Incidence of ED after ADT: 86% *vs.* 58% in RP patients *vs.* 43 in RT patients *vs.* 33% in patients undergoing watchful waiting ($P<0.0001$)
Potosky *et al.*[65]	2002	88 potent ADT patients 223 potent CaP patients on no treatment	80% of ADT patients reported ED after 1 year *vs.* 30% of those receiving no treatment ($P<0.001$)
Potters *et al.*[62]	2001	482 CaP patients potent before treatment	The 5-year actuarial potency rate was: • PPB alone: 76%; • EBRT+BT: 56% ($P=0.08$); • NAAD+BT: 52%; • EBRT+BT+NAAD: 29% ($P=0.13$) Pre-treatment use of NAAD and patient age predicted ED ($P=0.0001$ and 0.04, respectively).
Potosky *et al.*[49]	2001	132 orchiectomized CaP patients 299 CaP patients on LHRH agonists	51% of men with some interest in sex before treatment had no interest after treatment ~73% of men ceased engaging in sexual activity after treatment 69% of men who were potent before treatment were impotent after treatment No differences were observed based on type of ADT

Abbreviations: ADT, androgen deprivation therapy; BAT, bioavailable testosterone; BT, brachytherapy; CaP, prostate cancer; CI, confidence interval; CVOD, corporal veno-occlusive dysfunction (venous leak); EBRT, external beam radiotherapy; ED, erectile dysfunction; IIEF, International Index of Erectile Function; NAAD, neoadjuvant androgen deprivation; PPB, permanent prostate brachytherapy; RP, radical prostatectomy; RT, radiotherapy; T, testosterone; *vs.*, versus.

results of the animal studies cited above, testosterone may as well not be the only androgen associated with erectile function, as DHT and adrenal androgens, such as dehydroepiandrosterone and dehydroepiandrosterone sulfate, may play a significant role too.

Sexual desire

The impact of ADT on libido has been difficult to evaluate and measure, not the least reason for which is the absence of a validated tool for this. Sexual desire involves not only biological but also psychological mechanisms.[69] Those two facts make clear conclusions of the exact role of ADT on sexual desire difficult to draw. Nevertheless, in the aforementioned Prostate Cancer Outcomes Study, in which 431 men with various stages of prostate cancer on ADT were examined, the authors showed the proportion of men reporting no sexual interest increased from 28% to 67% after orchiectomy and from 32% to 58% after LHRH agonists.[49] In this study, 51% of men interested in sex before treatment reported 'no interest' after therapy and about 73% reported ceasing engaging in sexual activity after treatment, regardless of the type of ADT prescribed.[49] In the study by Marumo *et al.*,[50] despite the total suppression of sexual activity induced by the LHRH agonist treatment, none of the nine previously active sexual patients presented serious complaints concerning ED and total suppression of sexual activity. This was explained by a concomitant self-reported decrease in sexual desire following therapy in all patients. These results were not confirmed by the studies from Ahn *et al.*[55] and Martinez-Jabaloyas *et al.*[54] who found no relationship between testosterone levels and sexual desire.

As for erectile function, preservation of sexual desire in some prostate cancer patients on ADT suggests that either testosterone might not be the only hormone sustaining libido, and/or that brain receptors might have varying sensitivity to androgens too. As stated by Martinez-Jabaloyas *et al.*,[54] androgens are 'necessary but not sufficient' for normal sexual interest, and the testosterone threshold value below which libido is affected remains poorly defined.[57] It is our hypothesis that the different side effects of ADT on male sexual behavior happen at different testosterone threshold values. In the published studies,[55] the relationships between sexual desire and testosterone levels were shown to vary with age as well as they were less clear in elderly patients.

Penile morphology

In the study by Marumo *et al.*[50] the maximal circumferential increase at the tip and base of the penile shaft during erection was significantly decreased by the administration of LHRH agonist ($P<0.01$). This is likely the result of smooth muscle loss and collagenization of the corporal tissue with resultant penile contraction.

Ejaculation

In a study by Corona *et al.*,[70] after adjustment for confounders, perceived ejaculate volume reduction was specifically associated with the use of ADT as well as with different other medications. This is not surprising as seminal fluid production is dependent on testosterone to some extent. In the youngest age group, subjects with premature ejaculation have been reported to have higher total and free testosterone levels when compared to the other groups. Conversely, in the oldest age group, lower total and free testosterone levels were observed in delayed ejaculation subjects. Testosterone might play a facilitatory role in the control of ejaculatory reflex. Both central and peripheral mechanisms have been advocated to explain this association. Clinical studies are in progress to further establish the role of testosterone in the ejaculatory dysfunction, attempting to revert delayed ejaculation by androgen administration.

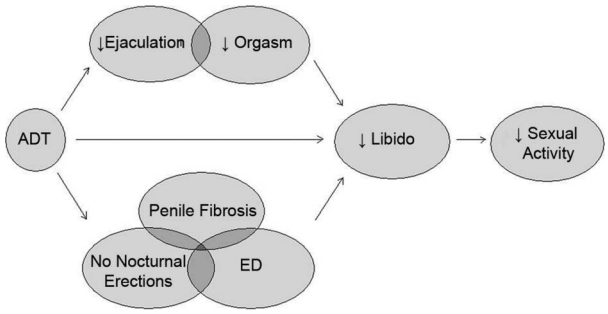

Figure 1 Consequences of ADT on patient's sexual function. ADT, androgen deprivation therapy; ED, erectile dysfunction.

Orgasm

In the study mentioned above by Ahn *et al.*[55] performed on a cohort of 213 patients with lower urinary tract symptoms, free testosterone levels were found to be correlated on regression analysis with orgasmic function ($r=0.179$, $P=0.02$) defined by the score at the items 9 and 10 of the IIEF questionnaire. In this study, the assessment method did not assess eventual associations of the free testosterone levels with orgasm or ejaculation separately. Further studies are required to determine the impact of ADT on orgasm and ejaculation, especially as the IIEF is a poor assessment tool for both (**Figure 1**).

CONCLUSION

Androgens play an essential role in maintaining sexual structures and their function at both the central and peripheral levels. In this setting, the overall side effects of ADT on sexual function can be significant, and the decreased sexual activity observed while on ADT may result from a large variety of sexual problems, which lead to an overall reduction in quality of life and self-esteem. Understanding the pathophysiological consequences of ADT on sexual function represents the initial step in defining the most efficient treatment options to relieve them.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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