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The effects of androgen depletion on human erectile function: a prospective study in male-to-female transsexuals

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The objective of the study was to determine the effects of androgen depletion on erectile function in a population of male-to-female transsexuals. The erectile function of 25 consecutive male-to-female transsexuals on androgen depletion treatment and scheduled for surgical gender reassignment was prospectively evaluated using medical and sexual history, physical examination, total serum testosterone, International Index of Erectile Function (IIEF-15) questionnaire, penile colour-coded Doppler ultrasonography (CDU) after pharmacological stimulation and nocturnal penile tumescence (NPT) test. All but one had undetectable or low testosterone. Subjective erectile function, according to IIEF-15 scores, and penile CDU findings did not correlate with testosterone levels, whereas NPT test findings correlated well with testosterone levels. These findings would suggest that nocturnal erections are androgen-dependent whereas sexually induced erections are androgen-independent. It can also be assumed that testosterone is important but not essential for male erectile function and that other androgen-independent pathways can be responsible for sexually induced erections.
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Introduction

Androgens play an important role in all stages of life. During embryonic period, they act to virilise the urogenital area, during puberty they dramatically contribute to development of male secondary sexual characters and start of spermatogenesis and sperm maturation, and during adult life they are essential for the expression of normal libido.

However, the exact role of androgens, particularly testosterone, in penile erection is not fully understood. Conditions like congenital or acquired hypogonadism and pharmacological or surgical castration for prostate cancer are known to be associated with significant decrease of both sexual interest and nocturnal erections. Nevertheless, more than 40% of hypogonadal or castrated patients maintain the ability of obtaining sexually induced erections as well as visually stimulated erections.[1,2] On the other hand, only 44% of men with acquired hypogonadism and erectile dysfunction (ED) benefit from androgen supplementation compared to 17% treated with placebo.[3]

Understanding the role of testosterone in penile erection is a major issue in the management of patients with ED, for both diagnostic and therapeutic purposes, particularly in ageing men who have a high prevalence of ED as well as of acquired hypogonadism.[4]

The aim of this study was to determine the effects of testosterone depletion on the erectile function (EF) in a population of 46 XY male suffering from gender dysforia, a condition known as male-to-female transsexualism.

Materials and methods

The study population consisted of 25 consecutive male-to-female transsexuals with a mean age of 32.6 y (range 21–52 y) scheduled for surgical gender reassignment at our institution between December 1996 and December 2000.

Patients underwent for a mean period of 55 months (range 29–96 months) pharmacological androgen suppression arranged by their endocrinologist and consisting of ciproterone acetate (100 mg/

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day orally) in 12, LHRH analogues in six, LHRH analogues + ciproterone acetate in six and finasteride (5 mg/day orally) in one. To induce female sex secondary characters, they also received estradiol, 100 mg/day transdermally.

Evaluation of EF, performed 1–3 weeks before surgery, consisted of medical and sexual history including the self-administered International Index of Erectile Function (IIEF-15) questionnaire, physical examination, measurement of serum levels of morning total testosterone, penile colour-coded Doppler ultrasonography (CDU) after pharmacological stimulation and nocturnal penile tumescence (NPT) test.[5]

Penile CDU was performed in a quiet room. Peak systolic velocity (PSV) and resistance index (RI) of left and right cavernous artery were measured 3, 10 and 20 min. after intracavernous injection of 20 μg PGE1, and erection scored by the investigator from 1 to 5 (1 = no tumescence, 2 = mild tumescence, 3 = good tumescence but not enough for intercourse, 4 = rigid enough for intercourse, 5 = full rigidity). Between second and third measurements the patient was left alone in the room and asked to perform manual genital stimulation. The test was considered reliable only if the patient obtained an erection equal to or better than that obtained at home.

The NPT test was performed for two consecutive nights with the Rigiscan Plus device (Dacomed, USA) and considered normal in the case of recording of at least four erectile events per night lasting at least 30 min, an increase in circumference ≥ 2 cm at the base and ≥ 2 cm at the tip, and maximal rigidity at both base and tip $\geq 60\%$.

All patients were fully informed about the study and gave a written consent. The Kruskal–Wallis test was used for statistical analysis of correlation.

Results

All patients completed the full assessment schedule.

Questions 2 and 4 of the IIEF-15 questionnaire were used for subjective determination of EF and the results are reported in Table 1. To determine whether or not hormonal depletion had caused subjective changes in EF, all patients were asked to state if they would have scored the same or better in IIEF questions 2 and 4 just before hormonal treatment. Interestingly, all of them reported their EF before hormonal depletion being comparable to their EF at the time of our evaluation.

Physical examination did not show any abnormality; all patients presented a normal penis, slight hypotrophy of testes and prostate, female fat and body hair distribution, and hormone-induced gynaecomastia.

Serum levels of morning total testosterone were found to be normal (4.5–8.5 ng/ml) only in the patient treated with finasteride, low (1–4.4 ng/ml) in 10 patients and undetectable (<1ng/ml) in 14 patients. As shown in Table 1, testosterone levels did not correlate with IIEF scores (*P*-value 0.7 for question 2 and 0.4 for question 4).

Penile CDU after pharmacological stimulation yielded normal results (PSV >35 cm/s, RI >0.9, erection score 4–5) in all patients, suggesting no correlation between pharmacologically induced erection and testosterone levels. Interestingly, the erection score was always upgraded after the period of manual genital stimulation, thus providing further information on the role of sexual stimulation in this group of patients.

The NPT test, conversely, yielded normal results in 12 patients, equivocal (sporadic, ie less than 4 rigid events per night) in seven, and pathologic (no rigid events at all) in six. Interestingly, NPT test results were strictly related ($P<0.006$) to serum testosterone levels (Table 1).

Discussion

Recent studies have shown that testosterone plays a role in almost all aspects of sexual function. Certainly, its main effect is central stimulation of sexual interest and such effect is mediated by metabolites, for example, oestrogens after the peripheral conversion of testosterone by aromatase, acting either directly or by modifying neural andro-

Table 1 Serum total testosterone levels compared to IIEF-15 questions 2 and 4, penile CDU and NPT test findings

Pts	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*
T	0.1	0.1	0.2	0.2	0.4	0.4	0.5	0.5	0.6	0.7	0.8	0.8	0.8	0.9	1	1.9	2	2.2	2.8	3	3.1	3.3	3.6	4	5.3
Q 2	3	4	0	4	2	2	5	4	5	4	2	5	3	1	0	3	5	5	1	2	5	3	1	2	4
Q 4	1	4	0	5	3	1	5	3	5	3	2	5	1	2	0	5	4	4	2	4	3	3	3	2	5
CDU	N	N	N*	N	N	N	N	N	N	N	N	N	N	N	N*	N	N	N	N	N	N	N	N	N	N
NPT	P	P	P	P	P	P	<	<	<	<	<	<	N	N	<	N	N	N	N	N	N	N	N	N	N

Serum testosterone levels *vs* IIEF-15 question 2: *P*-value 0.7 (ns); Serum testosterone levels *vs* IIEF-15 question 4: *P*-value 0.4 (ns); Serum testosterone levels *vs* NPT study: *P*-value <0.006. (Statistical analysis using the Kruskal–Wallis test). NPT: N = normal; P = pathologic; < = less than four rigid events. CDU: N = normal; N* = normal values but not full erection.

gen metabolism.[6] Another central effect of testosterone involves stimulation of dopamine release by the medial preoptic area (MPOA) with consequent activation of the dopaminergic erectile pathway.[7] Such effect is mediated by stimulation of nitric oxide synthetase (NOS) in the MPOA, which leads to an increase in nitric oxide (NO) production and, consequently, in dopamine release.[8]

The regulatory effect of testosterone on NOS expression and consequent NO production occurs also in the nonadrenergic noncholinergic (NANC) nerve fibres of corpus cavernosum, and is responsible for the peripheral (penile) action of this hormone. Studies in rats have demonstrated that NOS expression in the nerve fibres of corpus cavernosum is significantly reduced by castration and restored by subsequent androgen supplementation, suggesting that NO is an androgen-dependent neurotransmitter of penile erection.[9] This peripheral effect has been postulated as being responsible for loss of erection associated with medical or surgical castration.

The present study showed that nocturnal erections were strictly related to testosterone levels, suggesting their androgen dependency, whereas sexually induced erections did not correlate with testosterone levels, suggesting their androgen independence. These findings are in good agreement with the frequent occurrence of sexually induced erections and visually stimulated erections in castrated patients. Our findings are good in agreement also with those by Luisi and Franchi,[10] who demonstrated that testosterone depletion in young hypogonadal men was associated with decreased sexual interest and activity but normal response to visual erotic stimuli, and those by Carani *et al*,[11,12] and co-workers who demonstrated that testosterone supplementation enhanced rigidity and frequency of nocturnal erections but had no effect on sexually induced erections.

Taking together these information, it can be postulated that testosterone plays a major role in sexual interest and nocturnal erections, which definitely are androgen-dependent, but a little role in sexually induced erections, which seem to be androgen-independent. However, sexually induced erections can, in the long term, deteriorate because the decrease in sexual interest and nocturnal erections may lead to penile hypoxia and consequent fibrosis.[13] This would explain the limited response to testosterone supplementation (44% with treatment *vs* 17% with placebo) in men with acquired hypogonadism.[3] Interestingly, our patients reported their EF having not been deteriorated by hormonal depletion. This may be due to their young age and, probably, to their maintained sexual interest. Whether maintenance of sexual interest in this particular subset of patients is related to age, to gender dysforia itself or to the previously described central effects of oestrogens administered to these patients deserves further investigation.

In conclusion, testosterone plays an important but not essential role in male EF. Available data suggest the erectogenic effects of testosterone being mediated both centrally and peripherally by NO. Thus, other androgen-independent pathways, different from the androgen-dependent NO-cGMP pathway, can be involved in the maintenance of sexually induced erections in acquired hypogonadal men and should be investigated to provide alternative treatment options for such patients.

References

1 Rousseau L, Dupont A, Labrie F, Couture M. Sexuality changes in prostate cancer patients receiving antihormonal therapy combining the antiandrogen flutamide with medical (LHRH agonist) or surgical castration. *Arch Sex Behav* 1988; **17**: 87–98.
2 Greenstein A, Plymate SR, Katz PG. Visually stimulated erection in castrated men. *J Urol* 1995; **308**: 650–652.
3 Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol* 2000; **164**: 371–375.
4 Feldman HA *et al.* Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; **151**: 54–61.
5 Rosen RC *et al.* The International Index of Erectile Function (IIEF): a multidimension scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–830.
6 Dykeman DA, Katz LS, Foote RH. Behavioral characteristics of beef steers administered estradiol, testosterone and dihydrotestosterone. *J Anim Sci* 1982; **55**: 1303–1309.
7 Szczypka MS, Zhou QY, Palmiter RD. Dopamine-stimulated sexual behavior is testosterone dependent in mice. *Behav Neurosci* 1998; **112**: 1229–1235.
8 Du J, Hull EM. Effects of testosterone on neuronal nitric oxide sythetase and tyrosine hydroxylase. *Brain Res* 1999; **836**: 90–98.
9 Zvara P, Sioufi R, Schipper HM, Begin LR *et al.* Nitric oxide mediated erectile activity is a testosterone dependent event: a rat erection model. *Int J Impot Res* 1995; **7**: 209–219.
10 Luisi M, Franchi F. Double-blind group comparative study of testosterone undecanoate and mesterolone in hypogonadal male patients. *J Endocrinol Invest* 1980; **3**: 305–308.
11 Carani C, Scuteri A, Marrama P, Bancroft J. The effects of testosterone administration and visual erotic stimuli on nocturnal penile tumescence in normal men. *Horm Behav* 1990; **24**: 435–441.
12 Carani C, Granata AR, Bancroft J, Marrama P. The effects of testosterone replacement on nocturnal penile tumescence and rigidity and erectile response to visual erotic stimuli in hypogonadal men. *Psychoneuroendocrinology* 1995; **20**: 743–753.
13 Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. *Int J Impot Res* 1998; **10**: 113–120.