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Testosterone Therapy for Low Sexual Interest and Erectile Dysfunction in Men: A Controlled Study

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Summary: A double blind cross-over comparison of testosterone and placebo injection was carried out in two groups of men with normal circulating testosterone levels, 10 complaining principally of loss of sexual interest and 10 complaining principally of erectile failure. A significant increase in sexual interest was produced by testosterone in the first group. There was no effect on erectile function in either group. These results support previous findings from hypogonadal men that testosterone influences sexual interest but not erectile function, and indicate that increasing plasma testosterone can effect sexual interest even in men with pre-treatment testosterone levels within the normal range.

The therapeutic value of androgenic hormones in the treatment of male sexual dysfunction remains unclear. There is now unequivocal evidence from controlled studies of hypogonadal men that androgens are necessary for some aspects of normal male sexuality (Davidson *et al*, 1979; Skakkebaek *et al*, 1981; Luisi and Franchi, 1980). The most convincing and predictable androgen effects are on sexual interest or appetite, and ejaculation. Erection, by contrast, may not be primarily dependent on androgens. Hypogonadal men whose sexual interest and activity was low, have shown erectile responses to erotic stimuli in the laboratory which were no different to those of normal subjects and which did not increase, as the sexual interest and activity did, after androgen replacement (Bancroft & Wu, 1983; Kwan *et al*, 1983). Also, in a study of sexual offenders, suppression of sexual interest and activity by an anti-androgen, cyproterone acetate, was not associated with a suppression of erectile response to erotic films (Bancroft *et al*, 1974). Spontaneous erections, on the other hand, especially those occurring during sleep or on waking, are apparently reduced by androgen withdrawal (Kwan *et al*, 1983; O'Carroll, 1983). The physiology of sleep erections is not understood, but they are presumably responses to some central event, and it may be that it is this central process rather than the erectile mechanisms *per se* which is androgen dependent.

The amount of androgen required to maintain normal sexual function has not yet been established. Although there is some evidence of a dose-response relationship (Davidson *et al*, 1979; Salmimies *et al*, 1982; O'Carroll, 1983), the amount required appears to vary considerably from one individual to another. This is to be expected if we assume that there is genetic variability in target organ sensitivity to steroid hormones. It has been widely assumed that there is a threshold above which further increases in circulating androgen will have no behavioural effects. Apart from the fact that as yet there is no convincing evidence that this is the case, we still have to allow for considerable individual variation in the level of such a threshold. It may be below the "normal" range in some men and well within it in others. Wu *et al* (1982), in a study of Klinefelter men with testosterone levels in the lower part of the normal range, demonstrated a significant increase in sexual interest with testosterone administration. The only comparable evidence from normal subjects is from a World Health Organisation study of androgens as male contraceptives, where a slight increase in sexual interest was reported during testosterone administration (WHO, 1982).

From this evidence we hypothesised that androgen administration may be beneficial in treating loss of sexual interest in some men with normal levels of circulating testosterone, but not erectile dysfunction, unless it is secondary to low sexual interest. Unfortunately, evidence from studies of the effect of hormone administration in sexually dysfunctional men is inconclusive (Schiavi & White, 1976). In most cases no clear distinction has been made between men with loss of sexual interest and those with erectile failure. Two studies (Bruhl and Leslie, 1963; Jakobovitz, 1970) claim significant improvement with oral testosterone administration, but neither were reported with suffi-

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cient detail to allow proper evaluation. Cooper (1980) using a low dose of a synthetic androgen, mesterolone, and Benkert *et al* (1979) using testosterone undecanoate (T.U.), both failed to find any benefit of androgen over placebo. These were the only studies that assessed the effects of exogenous hormone administration on circulating plasma levels, and both failed to find any increase. In fact, Benkert *et al* (1979) reported that the only specific effect of T.U. treatment was to *decrease* the total plasma testosterone level. These results reflect the difficulty in producing sustained increases in plasma testosterone in eugonadal men because of the powerful homeostatic mechanisms which act to suppress endogenous androgen production and increase metabolic clearance (O'Carroll, 1983).

In the study reported here we have investigated a method of androgen administration, which has been shown to produce sustained rises in circulating levels (O'Carroll, 1983), in two distinct groups of dysfunctional men: (a) those whose principal complaint was loss of sexual interest; and (b) those with erectile dysfunction as their principal problem. Our prediction was that testosterone treatment would be beneficial for the first group but not the second.

Subjects and Methods

Subjects

Subjects were recruited from the sexual problem clinics in Edinburgh between May 1981 and December 1982. They were required to present either with loss of sexual interest or erectile dysfunction, and to have no evidence of liver or prostatic disease on biochemical tests. They were allocated to two groups as follows.

Group I – low sexual interest group: Presenting complaint of loss of sexual interest, not obviously secondary to erectile failure or physical or mental illness. Ten subjects were recruited in this group, ages 33 – 64 years (mean 44.6, S.D. 10.3). All were married with current sexual partners.

Group II – erectile dysfunction group: Presenting complaint of difficulty in achieving or maintaining a full erection during sexual activity, not secondary to loss of sexual interest or obvious physical or mental illness. Twelve subjects were recruited but two dropped out at an early stage, one because he found the intramuscular injections too painful, the other because of lack of response (he had received only placebo). There were therefore 10 subjects who completed the investigation, ages 19 to 64 years (mean 45.4, S.D. 13). Eight were married and nine had current sexual partners.

Design

An identical design was used for the two subject groups. Each subject was assessed for a four week baseline period. This was followed by 12 weeks of treatment, which consisted of fortnightly intramuscular injections of Sustanon (Sustanon – Organon. – testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, testosterone decanoate 100 mg) or matched placebo. Half the subjects in each group received six weeks of Sustanon followed by six weeks placebo, and the other half vice versa.

Assessment

Behavioural: a) *Daily diaries* – throughout the 16 weeks, a daily diary was completed by each subject. The diary, together with the instructions for its use are given in the Appendix. A record was made of the occurrence of waking erections, sexual activity (masturbation or activity with partner) who initiated activity, and whether ejaculation occurred. Sexual interest was measured by visual analogue scales for rating (1) frequency of sexual thoughts and (2) sexual excitement associated with such thoughts. Mood was also rated by 10 further visual analogue scales which are listed in the appendix. The baseline period allowed the subject to become accustomed to performing daily self-ratings. During this period the method of completing the diary was checked by the investigator; b) *Interview ratings* – based on a semi-structured interview, interviewer ratings of sexual interest, positive and negative feelings during sexual activity, non-genital sexual arousal, erections and ejaculatory control were made at the end of each treatment period for the previous six weeks. The rating scales used are shown in the Appendix. The interviewer was blind to the method of treatment.

Hormonal: Weekly blood samples were taken throughout the 16 weeks (hormone injections were given immediately following blood sampling). Plasma was stored at −20°C and later assayed for total testosterone (Corker and Davidson, 1978) and sex hormone binding globulin (SHBG) (Anderson *et al*, 1976).

Analysis of results: The effects of testosterone and placebo were compared in the following ways. Frequency of sexual activity etc. for the two six-week periods were directly compared by paired t-tests. Visual analogue ratings were first reduced to weekly means, and then compared across time periods using analysis of variance for repeated measures. Interview ratings were compared by means of the sign test. Plasma levels of testosterone and SHBG were compared by analysis of variance for repeated measures.

Results

Group I – low sexual interest

In comparing diary data for the two treatment periods, only one variable, the frequency of sexual thoughts, showed a significant testosterone effect ($P = <0.02$). This effect of testosterone was not transient, and ANOVAR showed no significant differences across time nor any significant interaction between treatment and time. This is shown graphically in the Figure 1. For this Figure, the visual analogue scores were standardised using the proportional method (Maxwell, 1978). The difference between each subject's weekly mean score and his overall entire study mean score was expressed as a percentage of the range of the scale used by that individual. All other sexual variables from the diary were higher during testosterone administration, but not significantly so (full details available on request). None of the mood ratings showed a significant effect.

Interview ratings for sexual interest and erection are shown in Table I. There was a weakly significant effect ($P = <0.1$) of testosterone on the sexual interest ratings. None of the other

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TABLE I

Effects of testosterone and placebo on interview ratings of sexual interest and erectile function in two groups of men

Behavioural rating	During testosterone administration	During placebo	Number improved with testosterone	Number worse with testosterone	Sign test
	Mean (S.D.)	Mean (S.D.)	Mean	Mean	
Group I: *low sexual interest* (n = 8)*					
Sexual Interest (0–6)	4.3 (1.0)	3.1 (1.9)	4	0	P<0.1
Erection (0–8)	7.6 (0.8)	7.7 (0.8)	1	2	NS
Group II: *erectile dysfunction* (n = 9)					
Sexual Interest (0–6)	5.0 (0.8)	4.9 (1.3)	2	2	NS
Erection (0–8)	5.6 (2.8)	4.7 (2.5)	3	1	NS

* Interview data was incomplete in 3 subjects

TABLE II

Effects of testosterone and placebo injections on plasma testosterone and SHBG in two groups of men

Hormone (nmol/L)	Base line (B)	Testosterone administration (T)	Placebo (P)	ANOVAR	
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)		
Group I: *low sexual interest* (n = 10)					
Testosterone	23.1 (7.0)	31.7 (13.9)	22.9 (7.0)	T>P T>B	P<0.01
SHBG	33.5 (10.5)	27.6 (8.8)	33.5 (10.5)	T<P T<B	P<0.05
Group II: *erectile dysfunction* (n = 10)					
Testosterone	16.8 (5.4)	20.5 (7.3)	14.3 (5.9)	T>P T>B	P<0.01 P<0.05
SHBG	30.4 (10.7)	24.3 (8.5)	27.7 (9.6)	T<P T<B	P<0.05
Group I v II (t-test)	Testosterone P<0.05 SHBG NS	% increase in testosterone NS			

ratings showed significant differences on the sign test. The testosterone and SHBG levels during the base line period and two treatment periods are shown in Table II.

Group II – erectile dysfunction group

Comparison of diary data for the two treatment periods showed no significant treatment effect on any variables, though all sexual variables were higher during testosterone administration. Comparison of interview ratings of sexual and erectile function is shown in Table I. None of the interview ratings showed significant treatment effects. The plasma concentrations of testosterone and SHBG during the base line and two treatment periods are shown in Table II.

Discussion

This study shows that, as predicted, substantial increases in testosterone levels in eugonadal men can increase sexual interest. The failure to improve sexual interest in the erectile dysfunction group can be attributed to a lack of scope for improvement in their case. No beneficial effect on erectile function was demonstrated.

This therapeutic effect of testosterone has to be qualified, however; in only three out of 10 subjects was it sufficient to be clinically judged as an adequate form of treatment. In the others, the changes were either small or did not generalise to the sexual relationship. This may be because our subjects varied in their target organ sensitivity to androgens, or, perhaps more importantly, in the manner in which external factors inhibited sexual interest or prevented its expression in

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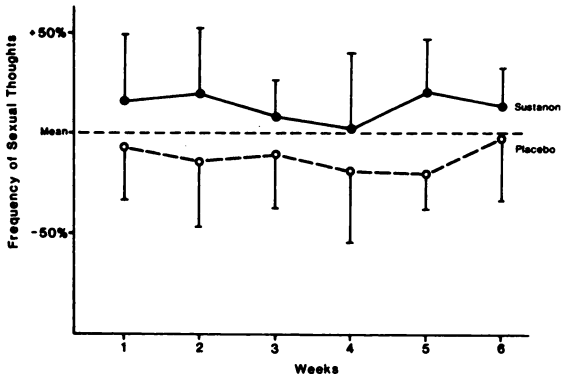


FIG 1.—Frequency of sexual thoughts, testosterone versus placebo treatment in ten men complaining of reduced sexual interest.

the relationship, e.g. communication difficulties, resentment, etc.

An unexpected finding was that the erectile dysfunction group had significantly lower testosterone levels during the baseline period. The proportional increase in testosterone during treatment was however very similar in the two groups. We cannot account for this finding, but it does reinforce out main conclusion—that androgens are relevant to sexual interest but not erectile function, as those men whose principal problem was erectile dysfunction failed to respond to testosterone therapy even though their testosterone levels were significantly lower than those in the low sex interest group.

More evidence is required about the characteristics of responders and non-responders, but at this stage we can cautiously conclude that testosterone therapy in sufficient dosage may have a modest contribution to make in the management of loss of sexual interest in men. This effect may be best exploited in some cases by combining it with appropriate counselling methods.

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Appendix

Instructions for using diary

I. Did you awake with an erection this morning? (please tick)

II. *Mood scales* (visual analogue) Please place a mark on the mood scale lines to indicate how you have felt today. A mark to the extreme left means "not at all" and a mark to the extreme right means "more so than I can ever remember".

1. Cheerful and happy, 2. Fatigued and tired; 3. Sociable and friendly; 4. Energetic; 5. Tense and anxious; 6. Irritable; 7. Changeable or up and down; 8. Aggressive; 9. Depressed and unhappy; 10. Relaxed.

III. *Sexual activity*

If no sexual activity occurred today, please tick box A. If one of the activities listed below occurred, then enter a number 1–4 in the appropriate box (M, A.C., and S.I.) to indicate how satisfactory you found it.

Activity

M – Masturbation; A.C. – Affectionate intimate contact with partner, i.e. caressing genital areas or breasts; S.I. sexual intercourse.

Rating

1 = unsatisfactory or even unpleasant
2 = neither satisfactory nor unsatisfactory
3 = quite satisfactory
4 = very satisfactory and pleasant

In the lower box marked E_1, simply insert a tick if you ejaculated on that occasion.

For activities A.C. and S.I. please indicate with a tick whether the activity was self-initiated (s), partner initiated (p) or initiated by both (b).

IV. *Sexual thoughts* (visual analogue scale)

A. Please indicate how often you have found yourself thinking sexy thoughts today by marking the line A in the appropriate place. A mark to the extreme left means "no sexual thoughts at all"and a mark to the extreme right means "sexual thoughts frequently".

B. If you have had any sexy thoughts today, please indicate how often you have found yourself having feelings of sexual excitement accompanying your thoughts by marking the line B in the appropriate place. A mark to the extreme left means "sexual thoughts not associated with feelings of sexual excitement" and a mark to the extreme right means "sexual thoughts frequently associated with feelings of sexual excitement".

(Copy of diary form available on request).

Interview ratings

1. *Level of sexual interest*

"How often during the past × weeks have you found yourself thinking about sex with any interest, appetite or desire. Would you say it was several times a day, a week, once or twice a month, or less?"

0. Thoughts about sex absent, or never associated with desire; 1. rarely (less than once a month); 2. about once a month; 3. less than once a week, more than once a month; 4. at least once a week; 5. several times a week; 6. at least once a day.

2. *Negative feeling during sexual contact*

"You have made love approximately × times in the last × weeks. On what proportion of these occasions have you felt, at some stage, any unpleasant, or anxious, or tense feelings during lovemaking?"

A. 0. Rarely has sexual contact without anxious feelings; 1. unpleasant feelings on about 75% of occasions; 2. unpleasant feelings on about 50% of occasions; 3. unpleasant feelings on about 25% of occasions; 4. rarely has unpleasant feelings.

B. *"How strong are these feelings?"* (show subject rating scale)

1. Very mild; 2. mild; 3. moderate; 4. strong; 5. very strong.

3. *Positive feelings during sexual contact*

"What proportion of these occasions did you feel were enjoyable, mainly pleasurable?"

0. No pleasure from sexual contact at any time; 1. experiences pleasure on about 25% of occasions; 2. experiences pleasure on about 50% of occasions; 3. experiences pleasure on about 75% of occasions; 4. rarely fails to experience pleasure.

4. *Sexual arousal (non-genital)*

"How often during the past × weeks when you have engaged in sexual contact have you found yourself getting generally aroused? By that I mean general excitement, skin or heart rate changes, semi-voluntary body movement, sweating, spontaneous noise, etc.?"

A. Frequency

0. Never; 1. rarely; 2. on about 25% of occasions; 3. on about 50% of occasions; 4. on about 75% of occasions; 5. rarely does not become aroused.

B. Strength (show subject rating scale)

0. Calm, no excitement, no general bodily changes; 1. slightly aroused, wanting to continue, little body movement; 2. moderately aroused, feeeling excited, less inhibited, moving body during lovemaking, breathing more rapidly; 3. strongly aroused, very excited, making some noises, moving involuntarily, not aware of things happening around you; 4. highly aroused, out of control of your body, making loud noises, extremely active bodily movements. Unaware of anything going on around you, close to "passing out".

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5. *Erection*

"Do you have any difficulty in getting or keeping an erection during lovemaking?"

0. Never has an erection whilst awake; 1. only experiences erection on waking; 2. gets erection, but never during sexual contact with partner; 3. gets erection during loveplay, but insufficient for vaginal intercourse; 4. gets erection sufficient for vaginal intercourse but only when it is not expected to happen; 5. gets erection sufficient for vaginal intercourse on approximately 25% of occasions; 6. gets erection sufficient for vaginal intercourse on approximately 50% of occasions; 7. gets erection sufficient for vaginal intercourse on approximately 75% of occasions; 8. rarely unable to have vaginal intercourse.

6. *Premature ejaculation*

"During intercourse, are you able to control your ejaculation as you would like?"

0. Always ejaculates before or at time of vaginal entry; 1. nearly always ejaculates within 30 seconds of vaginal entry; 2. can usually delay ejaculation beyond 30 seconds, but not adequate control; 3. occasionally has adequate control; 4. adequate control on about 25% of occasions; 5. adequate control on about 50% of occasions; 6. adequate control on about 75% of occasions; 7. rarely fails to have adequate control; 8. can be delayed but partner urges rapid conclusion.

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