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Testosterone Treatment in Men with Erectile Disorder and Low Levels of Total Testosterone in Serum

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Since decreased serum levels of testosterone (T) do not necessarily predict good outcome of testosterone treatment for erectile disorder, the purpose of this study was to determine which men with erectile disorder and decreased serum levels might benefit from treatment. From a sample of 31 men ($\bar{x}$ age = 39 years), 15 (48%) with erectile disorder and decreased serum levels of T responded well after 8 weeks of testosterone treatment (100 mg of testosterone propionate in the sustained-release form given im once a week). Good treatment outcome was associated with several variables, but only high levels of luteinizing hormone (LH) and low values of the T/LH (testosterone/LH) ratio consistently emerged as significant correlates and/or predictors of effective treatment. Levels of LH above 7.5 IU/L or the values of the T/LH ratio equal to or below 0.87 nmol/IU in patients with erectile disorder and decreased serum levels of T suggest that testosterone treatment may be effective.

KEY WORDS: erectile disorder; impotence; testosterone; luteinizing hormone; testosterone/luteinizing hormone ratio.

INTRODUCTION

Decreased levels of serum testosterone may cause a decrease in men's sexual desire, which may subsequently impair their sexual arousal and cause erectile disorder. Such sexual dysfunction may respond to treatment with

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testosterone (Benson, 1994; Carani *et al.*, 1990; Gooren and Rubens, 1987; Kwan *et al.*, 1983; National Institutes of Health [NIH], 1992; O'Carroll *et al.*, 1985).

Men with a decreased sexual desire are usually not aware of it in the beginning and are more likely to be troubled by a gradually developing erectile disorder. In middle-aged men who develop such a dysfunction, it is particularly important to determine whether its cause is hormonal. Therefore, testosterone serum levels should be measured in such individuals, even though most men who seek help in sexual disorder clinics do not have a hormonal origin of their erectile disorder (Benson, 1994; NIH, 1992).

In view of the clinical observation that some men with erectile disorder respond to testosterone treatment, while others do not, the purpose of this study was to determine which men with erectile disorder and decreased serum levels of total testosterone might benefit from this treatment. We sought to elucidate those factors that are associated with good outcome of testosterone treatment for erectile disorder.

METHODS

Thirty-one men with erectile disorder and low serum levels of testosterone (T) participated in the study. They all sought help in the Sexual Disorders Clinic of the Clinical and Hospital Center "Dr. Dragisa Misovic" in Belgrade over a 3-year period (1990–1993) and were evaluated by one of us (Z.R.). The mean age of these patients was 39.25 years (SD = 7.57; range = 24–56). The majority (64.5%) were educated at the secondary school level.

Erectile disorder was diagnosed on the basis of the DSM-III-R criteria (American Psychiatric Association, 1987). An intact capacity for penile erection was verified by the Prostin VR test (Upjohn Co.), so that it was not necessary to verify it additionally by measuring nocturnal erections. Moreover, to exclude other causes of erectile disorder, patients were selected on the basis of normal findings on the following: general physical examination, routine laboratory analyses, laboratory analyses of liver and renal function, assessment of hormonal status (thyroid, pituitary, and adrenal function tests), urological examination, examination of penile blood vessels, and analysis of chromosomes (karyotype). These procedures were performed by clinicians who did not participate in other stages of the study.

Information was collected about any medications the patients might have been taking before the onset of erectile disorder and in the course of it. Those patients who were taking medications that are known to cause sexual dysfunction were excluded.

To monitor and assess the patients' sexual activity, only those subjects were included in the study who maintained the same sexual partner throughout the duration of the erectile disorder, including the treatment period.

A comparison (control) group consisted of 16 male volunteers, most of them hospital employees. They were subjected to the same evaluation procedures (physical examinations, laboratory analyses and assessments) as patients. Their mean age was 42.37 years (SD = 7.65; range = 31–59). The majority of these individuals (56.25%) also had a secondary education. There were no significant differences between patients and controls in terms of the basic demographic variables.

Procedures

The serum levels of T and luteinizing hormone (LH) were determined in the morning (at 8 AM) for 3 consecutive days in all patients and control group subjects. Results of these three measurements were expressed as mean levels. The T serum levels were measured by the means of the RIA method, according to a modification with extraction, provided by Biodata (Italy). Serum LH levels were also measured by the RIA method, in accordance with the modification provided by INEP-Zemun (Belgrade).

The mean value for intra-assay variability for LH was 7.15 IU/L (SD = 0.36) and the coefficient of variability (CV) = 4.99%. The mean value for interassay variability for LH was 7.45 IU/L (SD = 1.24, CV = 9.86%). For intra-assay variability for testosterone, $\bar{x}$ = 1.160 ng/ml (3.944 nmol/L), SD = 0.031 ng/ml (0.103 nmol/L), and CV = 2.7%. Finally, for interassay variability for testosterone, $\bar{x}$ = 0.506 ng/ml (1.520 nmol/L), SD = 0.033 ng/ml (0.112 nmol/L), and CV = 6.5%.

Normal T levels in the serum ranged from 12 to 35 nmol/L, while normal serum LH levels ranged from 1.05 to 10.5 IU/L. We have used the T/LH ratio to obtain a measure that would take into account variations in the levels of T and LH.

Thirty-one patients with low testosterone levels in serum were treated with testosterone propionate in the sustained-release form. The dosage was 100 mg im once a week for 8 weeks.

The main indicator of sexual activity was frequency of sexual intercourse, because information on that could be reliably obtained from both the patients and their sexual partners. Likewise, the key parameter of improvement in the treatment of erectile disorder was frequency of *successful* sexual intercourse (with normal erection), as reported by both partners. Information was also obtained on levels of sexual interest, sexual dreams

and fantasies, and spontaneous and nocturnal erections, but these were considered less objective for the purpose of rating sexual activity.

Sexual activity in the course of the treatment was continuously monitored by the second author (V.S.), who did not perform initial patient evaluations. He assessed sexual activity and outcome of an 8-week testosterone treatment using a 3-point scale based on the frequency of successful sexual intercourse, as reported by both partners. The following rating system was used: 0 = No improvement in sexual activity (no successful sexual intercourse, with persistence of erectile disorder); 1 = slight improvement in sexual activity (at least one successful sexual intercourse in the 15-day period preceding the assessment); 2 = obvious improvement in sexual activity (the frequency of successful sexual intercourse returns to that which was usual for the couple before the onset of erectile disorder).

Statistical Analyses

Student's *t* test for independent groups and the chi-square test were used for comparisons of independent variables between patients and controls. Pearson's correlation coefficient was used to examine the relationships between all variables within the group of patients and the control group. Stepwise discriminant analysis (Afifi and Clark, 1984) was performed with the aim of identifying variables that are significantly associated with good outcome of the testosterone treatment. The sensitivity analysis (Weinstein and Fineberg, 1990) was used for the purpose of determining the levels of hormones that might distinguish between responders and nonresponders to the testosterone treatment.

RESULTS

Good outcome of the testosterone treatment (defined as "obvious improvement in sexual activity") after 60 days of treatment was demonstrated in 15 (48.4%) patients. Poor outcome (defined as "no improvement in sexual activity, with persistence of erectile disorder") was found in 16 (51.6%) patients. There were no patients with slight improvement in sexual activity at the end of the treatment.

The mean age of patients with good outcome of treatment was 41.00 years (SD = 6.46); the mean age of patients with poor outcome of treatment was 37.63 years (SD = 8.35).

Table I compares several variables between the patients and the control group. In comparison with the control group, the mean level of T was significantly lower and the mean level of LH was significantly higher in the

patients. As a result, the mean T/LH ratio was significantly lower in the patients. Patients were significantly younger at the age they married.

In the control group, the Pearson correlation coefficient suggested a significant linear relationship between the levels of T and age at which the persons married ($r = -.519$). In the patients group, the following linear relationships (based on the Pearson correlation coefficients) were significant: Between higher levels of LH and good outcome of treatment ($r = .796$), between lower values of the T/LH ratio and good outcome of treatment ($r = -.629$), between gradual onset of erectile disorder and higher levels of LH ($r = .455$), between gradual onset of erectile disorder and onset of the disorder at a later age ($r = .378$), and between gradual onset of erectile disorder and good outcome of treatment ($r = .571$).

Using the Pearson correlation coefficient, the same (repeated) relationships between T and LH were not found in both the patient group and the control group.

Table II shows the results of the first discriminant analysis. It included all variables except for the T/LH ratio, which is not an independent variable. Variables associated with good outcome of treatment were higher levels of LH, greater number of children, older age (at the time when the hormone levels were determined), and gradual onset of erectile disorder. The correct classification index with such combination of variables was maximal: 100%.

Table III shows the results of the second discriminant analysis, which excluded the levels of T and LH, but included the T/LH ratio along with other variables. In descending order of significance, variables associated with good outcome of treatment were lower values of the T/LH ratio, older age (at the time when the hormone levels were determined), lower educational level, younger age at marriage, and younger age at the onset of masturbation. Poor outcome of treatment was associated with shorter duration of erectile disorder and onset of sexual activity at a later age. The correct classification index with this combination of variables was somewhat less informative: 96.15%.

Different results of the two discriminant analyses may be accounted for by the relationships between variables (as determined by the Pearson correlation coefficients), differences in the correct classification indexes, and greater prognostic value of the LH level than the T/LH ratio.

The sensitivity analysis showed that good outcome of treatment was associated with levels of LH higher than 7.5 IU/L and T/LH ratio equal to or lower than 0.87 nmol/IU. Therefore, it is reasonable to expect good outcome of the testosterone treatment in patients with decreased levels of T if their levels of LH are above 7.5 IU/L and their T/LH ratios are below the corresponding value.

Table I. Comparisons Between Patients Treated with Testosterone and Control Group Subjects

Variables	Patients (n = 31)			Control group (n = 16)		
	$\bar{x}$	SD	Range	$\bar{x}$	SD	Range
Age at which hormone levels were determined (years)	39.25	7.56	24–56	42.37	7.65	31–59
Educational level (1 = elementary school level; 2 = secondary school level; 3 = college level)	2.16	0.58	1.0–3.0	2.19	0.66	1.0–3.0
Age at onset of masturbation (years)	14.75	2.06	11.0–18.0	14.37	2.06	12.0–18.0
Age at onset of partner sexual activity (years)	19.16	2.91	16–30	18.81	1.9	16–22
Age at marriage (years)	24.03[b]	3.95	16–36	27.81	2.94	23–33
No. of children	1.54	1.26	1.0–7.0	1.43	0.62	1.0–2.0
Total testosterone (T) levels (nmol/L)	7.33[b]	1.41	4.5–9.4	16.96	5.7	12.1–35
LH levels (IU/L)	7.92[a]	4.01	1.6–18.7	6.05	1.32	4–8.6
T/LH ratio (nmol/IU)	1.24[b]	0.89	0.26–5	2.92	1.28	1.6–5.5
Age at onset of erectile disorder (years)	35.1	8.09	21–54			
Duration of erectile disorder (years)	4	3	1.0–17.0			
Mode of onset of erectile disorder (1 = abrupt; 2 = gradual)	1.74	0.44	1.0–2.0			

[a]Significant difference between patients and control group subjects ($p < 0.05$).
[b]Significant difference between patients and control group subjects ($p < 0.01$).

Table II. Significant Variables in Predicting Outcome of Testosterone Treatment—Results of the First Discriminant Analysis

Variables (by order of entrance)	Wilks's λ[a]	SCDF coefficients[b]	Good outcome of treatment		Poor outcome of treatment	
			$\bar{x}$	SD	$\bar{x}$	SD
LH levels	.31	1.057	10.8	2.57	4.68	1.57
No of children	.26	0.525	1.85	0.7	1.61	0.5
Age	.23	0.332	41.9	6.25	37.9	8.2
Mode of onset of erectile disorder (1 = abrupt, 2 = gradual)	.218	0.266	2	0	1.54	0.5

[a]Level of significance for all lambdas is < .001.
[b]Standardized Canonical Discriminant Function.

Table III. Significant Variables in Predicting Outcome of Testosterone Treatment—Results of the Second Discriminant Analysis

Variables (by order of entrance)	Wilks's λ[a]	SCDF coefficients[b]	Good outcome of treatment		Poor outcome of treatment	
			$\bar{x}$	SD	$\bar{x}$	SD
T/LH ratio	.585	1.3	0.69	0.16	1.89	1.03
Age	.458	0.669	41.9	6.2	37.9	8.2
Level of education	.419	0.656	2.08	0.49	2.38	0.65
Age at marriage	.388	0.611	23.54	2.57	25.31	4.90
Duration of erectile disorder	.367	−0.597	4.31	4.98	3.76	3.00
Age at onset of partner sexual activity	.33	−0.45	18.9	2.39	19.2	3.78
Age at onset of masturbation	.3	0.437	14.0	2.00	15.0	1.73

[a]Level of significance for all lambdas is < .001.
[b]Standardized Canonical Discriminant Function.

DISCUSSION

Even though levels of LH were higher in the group of patients as a whole (which was expected because patients had low levels of T), LH values showed prominent variability, ranging from 1.6 IU/L to 18.7 IU/L. In contrast, LH values in the control group were far more consistent, ranging from 4 IU/L to 8.6 IU/L. This indicates that in terms of LH levels, the group of patients was quite heterogeneous.

Levels of free testosterone, which is a biologically active form of the hormone (Carani *et al.*, 1990; Davidson *et al.*, 1983; Gooren and Rubens,

1987; Vermeulen *et al.*, 1972), were not determined in our laboratory. Some studies (Carani *et al.*, 1990) suggest that a decrease in the level of total testosterone does not automatically imply a decrease in the level of free testosterone. This might help account for the observation that increased levels of LH were not found in some of our patients with low levels of T, and that these patients did not respond to the testosterone treatment.

Discriminant analyses suggest that higher levels of LH and lower values of the T/LH ratio are most significantly associated with good outcome of testosterone treatment, and therefore they might predict good response. The same variables were identified as significant on the basis of the Pearson correlation coefficients.

A significant correlation was found between gradual onset of erectile disorder on one hand, and higher LH levels, somewhat older age, and good outcome of testosterone treatment, on the other. This finding suggests that patients with gradual onset of erectile disorder tend to have idiopathic hypogonadism and, therefore, they may be more likely to respond to testosterone treatment. However, our results also show that such a relationship is not the rule.

In men over 40 with gradual onset of erectile disorder and good outcome of testosterone treatment, which suggests a hormonal origin of erectile disorder (idiopathic hypogonadism), there may be an unusually early onset of andropause. Such a condition had been described more than 50 years ago in a few men in their early 40s (Werner, 1939). Although some authors disagree that it exists (Skolnick, 1992), it may reflect a genetically determined process of premature aging.

Good outcome of testosterone treatment was also associated with greater number of children in the first discriminant analysis. This was probably an artifact, because most patients with good treatment outcome had one or two children; there was only one patient with seven children. Likewise, the second discriminant analysis identified lower educational level and earlier age at which patients married as variables associated with good treatment outcome. It appears that these two variables are related, since persons with less education tend to marry earlier. However, it is difficult to conceptualize a meaningful relationship between lower educational level and erectile disorder with decreased levels of testosterone; therefore, the association of this variable with good outcome of treatment in a relatively small number of patients does not appear convincing.

The association of good treatment outcome with an earlier age of onset of masturbation does not appear to be clinically significant. Although an earlier age of onset of masturbation points to a stronger sexual drive (Kinsey *et al.*, 1948), the latter seems unrelated to the development of idiopathic hypogonadism later in life.

Poor outcome of testosterone treatment does not point with certainty to any particular cause of erectile disorder, and its etiology then requires further investigation.

In conclusion, the diagnostic workup of all middle-aged men who develop erectile disorder should include measurement of the serum levels of T and LH. The decision to start testosterone treatment should be based on the levels of LH and values of the T/LH ratio, because decreased levels of serum testosterone per se may not be the cause of erectile disorder and do not necessarily predict good outcome of treatment. According to the results from our laboratory, levels of LH above 7.5 IU/L or the values of the T/LH ratio equal to or below 0.87 nmol/IU in patients with erectile disorder and decreased levels of serum testosterone, suggest that the testosterone treatment is more likely to be effective and should therefore be attempted.

REFERENCES

Afifi, A. A., and Clark, V. (1984). *Computer-Aided Multivariate Analysis,* Lifetime Learning Publications, Belmont, CA.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed., rev., American Psychiatric Association, Washington, DC.

Benson, G. S. (1994). Endocrine factors related to impotence. In Bennett, A. H. (ed.), *Impotence. Diagnosis and Management of Erectile Dysfunction,* W. B. Saunders, Philadelphia, pp. 31-41.

Carani, C., Zini, D., Baldini, A., Della Casa, L., Ghizzani, A., and Marrama, P. (1990). Effects of androgen treatment in impotent men with normal and low levels of free testosterone. *Arch Sex. Behav.* 19: 223-234.

Davidson, J. M., Chen, J. J., Crapo, L., Gray, G. D., Greenleaf, W. J., and Catania, J. A. (1983). Hormonal changes and sexual function in aging men. *J. Clin. Endocrinol. Metab.* 57. 71-77.

Gooren, L., and Rubens, R. (1987). Overview of the concept of andropause. In Zichella, L., Whitehead, M., and Van Keep, P. A. (eds.), *The Climacteric and Beyond: The Proceedings of the Fifth International Congress on the Menopause,* Parthenon Publishing Group, Sorrento, pp. 85-93.

Kinsey, A. C., Pomeroy, W. B., and Martin, C. E. (1948). *Sexual Behavior in the Human Male.* W. B. Saunders, Philadelphia.

Kwan, M., Greenleaf, W. J., Mann, J., Crapo, Z., and Davidson, J. M. (1983). The nature of androgen action on male sexuality: A combined laboratory-self-report study in hypogonadal men. *J. Clin. Endocrinol. Metab.* 57: 557-562.

National Institutes of Health. (1992, Dec. 7-9). Impotence. *NIH Consensus Statement. 10*(4):1-31.

O'Carroll, R., Shapiro, C., and Bancroft, J. (1985). Androgens, behavior and nocturnal erection in hypogonadal men: The effects of varying the replacement dose. *Clin. Endocrinol.* 23: 527-538.

Skolnick, A. A. (1992). Is "male menopause" real or just an excuse? *J. Am. Med. Assoc.* 268: 2486.

Vermeulen, A., Rubens, R., and Verdonck, L. (1972). Testosterone secretion and metabolism in male senescence. *J. Clin. Endocrinol. Metab.* 34: 730-735.

Weinstein, M. C., and Fineberg, H. V. (1990). Structuring clinical decisions under uncertainty. In Weinstein, M. C., and Fineberg, H. V. (eds.), *Clinical Decision Analysis*, W. B. Saunders, Philadelphia, pp. 61-62.
Werner, A. A. (1939). Male climacteric. *J. Am. Med. Assoc.* 112: 1441-1443.