0021-972X/95/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 80, No. 12
Printed in U.S.A.

Effect of Raising Endogenous Testosterone Levels in Impotent Men with Secondary Hypogonadism: Double Blind Placebo-Controlled Trial with Clomiphene Citrate

ANDRE T. GUAY, SUDHIR BANSAL, AND GERALD J. HEATLEY

Section of Endocrinology (A.T.G.) and Biostatistics (G.J.H.), Lahey Clinic, Burlington, Massachusetts 01805; and the Section of Endocrinology, Brown University School of Medicine (S.B.), Providence, Rhode Island 02940

ABSTRACT

Secondary hypogonadism is not an infrequent abnormality in older patients presenting with the primary complaint of erectile dysfunction. Because of the role of testosterone in mediating sexual desire and erectile function in men, these patients are usually treated with exogenous testosterone, which, while elevating the circulating androgens, suppresses gonadotropins from the hypothalamic-pituitary axis. The response of this form of therapy, although extolled in the lay literature, has usually not been effective in restoring or even improving sexual function. This failure of response could be the result of suppression of gonadotropins or the lack of a cause and effect relationship between sexual function and circulating androgens in this group of patients. Further, because exogenous testosterone can potentially increase the risk of prostate disease, it is important to be sure of the benefit sought, *i.e.* an increase in sexual function.

In an attempt to answer this question, we measured the hormone levels and studied the sexual function in 17 patients with erectile dysfunction who were found to have secondary hypogonadism. This double blind, placebo-controlled, cross-over study consisted of treatment with clomiphene citrate and a placebo for 2 months each.

Similar to our previous observations, LH, FSH, and total and free testosterone levels showed a significant elevation in response to clomiphene citrate over the response to placebo. However, sexual function, as monitored by questionnaires and nocturnal penile tumescence and rigidity testing, did not improve except for some limited parameters in younger and healthier men.

The results confirmed that there can be a functional secondary hypogonadism in men on an out-patient basis, but correction of the hormonal status does not universally reverse the associated erectile dysfunction to normal, thus requiring closer scrutiny of claims of cause and effect relationships between hypogonadism and erectile dysfunction. (*J Clin Endocrinol Metab* **80:** 3546–3552, 1995)

FOR MANY YEARS, investigators have tried to define a male counterpart to the female menopause (1, 2), and after much debate for the past 2 decades, it has become clear that levels of testosterone decrease slowly in men after the age of 40 yr (3). Further, the fall is greater in the free fraction of testosterone because of a rise in sex hormone-binding globulin (4).

Although considerable lowering of male hormone has been associated with decreased libido and decreased ability to achieve spontaneous erections (5, 6), the minimum level of testosterone needed to maintain it is not really known. Further, exogenous testosterone showed an improvement in libido and nocturnal penile tumescence in younger hypogonadal men (7–9) but did not have similar effects in eugonadal men (10).

Organic impotence increases steadily in men more than 50 yr of age and can be multifactorial (11), and a number of these men have been found to have low or low normal androgens. After careful study, when a cause and effect was not found between the low testosterone levels and sexual dysfunction, the researchers (12) suggested that the two conditions should be evaluated separately because they are separate conditions. When the benefit of elevating the slightly low testosterone levels in elderly men was studied by using exogenous testosterone, it raised the hematocrit as well as the prostate-specific antigen level, but positive changes in sexual function were not mentioned (13).

We (14) previously reported a group of men examined for impotence, who, along with mildly low testosterone levels, did not have elevated gonadotropin levels and in whom endogenous testosterone levels could be restored to the normal range by the use of clomiphene citrate. Our current work is designed to study the effect of raising the levels of circulating testosterone without suppressing the hypothalamic-pituitary axis on libido and erectile function. During a recent consensus conference it was decided that such studies were needed in the area of sexual function in aging men (15).

Subjects and Methods

Subject selection

Men were considered candidates for this study when they had the complaint of erectile dysfunction for 6 or more months and low serum free testosterone levels and normal (or unstimulated) serum gonadotropin levels in an early (0800–1000 h) sample. An overlap was permitted in the normal range for serum total testosterone; although the normal range was greater than 250 ng/dL, patients were accepted for study when the level was equal to or less than 275 ng/dL. This was to compensate for the higher sex hormone-binding globulin level seen in older men. All candidates had normal results on magnetic resonance image

Received September 23, 1994. Revision received May 4, 1995. Accepted June 6, 1995.

Address all correspondence and requests for reprints to: Dr. André T. Guay, Section of Endocrinology, Lahey Clinic North, 1 Essex Center Drive, Peabody, Massachusetts 01960.

* Presented in part at the 75th Annual Meeting of The Endocrine Society, Las Vegas, NV, June 1993. This was supported in part by a grant from the Eleanor Naylor Dana Charitable Trust (New York, NY).

studies of the hypothalamic-pituitary axis. They all had normal levels of serum PRL, estradiol, and sex-hormone binding globulin.

Nocturnal tumescence and rigidity testing

Twenty-five men met the initial criteria, and they were screened with nocturnal penile tumescence and rigidity testing with the portable RigiScan monitor (Dacomed Corp., Minneapolis, MN). The results were automatically documented quantitatively with a software analysis package supplied by Dacomed. Although no clear consensus exists on which measured parameters are best to monitor, we chose what appeared to be the best overall measures of tumescence and rigidity: average maximum rigidity of the tip lead, average maximum tumescence of the base lead, change in tumescence at the base, total area under the curve of the tip lead rigidity, and total area under the curve of base lead tumescence.

Four men (16%) with normal nocturnal tracings were rejected for study because they were proven to have psychological impotence. Of the remaining 21 men who qualified, 2 declined the study, 1 withdrew during the study, and 1 was deleted from the study for not following the protocol. Seventeen men qualified and completed the study. The demographic data are listed in Table 1.

Questionnaires

Patients were asked to fill out detailed questionnaires that included sexual satisfaction assessment, global sexual satisfaction index, and frequency of sexual activity. These questionnaires were completed before the study and after each study phase. The sexual satisfaction assessment is based on scoring 12 statements answered true or false, with 1 point being awarded for each answered true. The total score reflects overall satisfaction, with 12 being the highest and 0, the lowest. The global sexual satisfaction index is a rating scale on how satisfying the sexual relationship is and is rated 0–8, with 8 being "could not be worse." The frequency of sexual activity provides a frequency score as recalled by the patient in being involved in sexual activities on a monthly basis, namely kissing, intercourse, masturbation, and sexual fantasy. A score of actual *vs.* perceived ideal frequency of intercourse provided an assessment of performance over desire.

Stimulation tests

As part of the initial screening, the functional capacity of the pituitary gland was tested with an iv bolus of GnRH (100 μg); LH and FSH were measured at baseline and 30 and 60 min after the injection. The hypothalamus was stimulated with a clomiphene challenge test using clomiphene citrate (50 mg, orally, twice a day for 7 days), and LH, FSH, total testosterone, and free testosterone were measured at baseline and on days 7 and 10.

Drug treatment

During the treatment phase, patients were selected to receive either clomiphene citrate (50 mg) or a placebo on Monday, Wednesday, and Friday by computer randomization in double blinded fashion. Patients were given drug A for 8 weeks and, after a washout of 2 weeks, were given drug B for 8 weeks (clomiphene citrate and an exact matching placebo were supplied by Marion Merrell Dow, Kansas City, MO). During treatment with drugs A and B, serum levels of LH, FSH, total testosterone, and free testosterone were measured on Friday morning at the end of the first and second months within 2 h of taking the last tablet of clomiphene or placebo.

After each drug was given, the patient was asked about sexual function and libido and whether he thought the tablet was the active drug or the placebo. Nocturnal penile testing was also carried out after each drug phase, and the questionnaires were filled out again. Although nocturnal penile tumescence measures the ability to respond, the questionnaires monitored actual performance as well as sexual desires.

Statistical analysis

Challenge tests were analyzed using an analysis of variance with repeated measures (BMDP2V Statistical Software, Los Angeles, CA). Treatment data and RigiScan and questionnaire results were analyzed using one-way analysis of variance. *Post-hoc* testing for significant pairs was performed using the Scheffe's test (BMDP7D Statistical Software). Contingency tables were analyzed using the Fisher exact test or a χ^2 analysis, as appropriate. In all instances, probability is two-tailed, with $P < 0.05$ regarded as statistically significant.

Laboratory testing

Hormonal measurements were made using standard RIA kits in the RIA laboratory at the Lahey Clinic. An exception was the sex hormone-binding globulin assay, which was performed by Nichols Institute (Tarzana, CA).

Of special note were the assays for LH, FSH, total testosterone, and free testosterone. The LH and FSH assays were performed with materials from Becton Dickinson Immunodiagnostics (Orangeburg, NY), in which goat antirabbit antiserum is used. The LH standards are calibrated against the WHO First International Reference Preparation (68/40) of pituitary human LH for immunoassay; the FSH standards are calibrated against the WHO Second International Reference Preparation of human FSH (78/549) in a single antibody system. The calculated sensitivities are 1.0 mIU/mL for LH and 0.3 mIU/mL for FSH. The interassay variations are based on results from lyophilized human serum-based controls. For the LH mean (±SD) of 9.38 ± 0.92 mIU, the coefficient of variation was 9.8%; for the mean of 36.40 ± 1.70 mIU, the coefficient of variation was 4.7%; for the FSH mean of 2.92 ± 0.36 mIU, the coefficient of variation was 12.3%; for the mean of 11.82 ± 0.76 mIU, the coefficient of variation was 6.4%.

The total testosterone analysis was performed with materials from Binax (Portland, ME) in a standard, double antibody RIA method using rabbit (antihuman) testosterone antiserum. The second antibody is goat (antirabbit) γ-globulin. The testosterone standard is a solution of 2000 ng/dL testosterone in a human serum base. The interassay variations are based on results from lyophilized human serum-based controls. For the total testosterone mean of 53.15 ± 4.45 ng/dL, the coefficient of variation was 8.4%; for the mean of 607.08 ± 39.92 ng/dL, the coefficient of variation was 6.6%.

The free testosterone analysis was performed with materials from Diagnostic Products Corp. (Los Angeles, CA). It is a direct, or single tube assay, not calculated as a function of total testosterone and sex hormone-binding globulin, and uses polypropylene tubes coated with rabbit antibodies to free testosterone. The standards are various concentrations of free testosterone (0–50 pg/mL) in human serum. The interassay variations are based on results from lyophilized human serum-based controls. For the free testosterone mean (±SD) of 3.15 ± 0.32 pg/mL, the coefficient of variation was 10.3%; for the mean of 14.53 ± 1.16 pg/mL, the coefficient of variation was 8.07%.

Results

Seventeen men, with a median age of 60.5 yr (range, 42–71 yr), completed the study. The detailed baseline hormone data are listed in Table 2.

GnRH stimulation

Stimulation of pituitary function in the men (n = 17) with GnRH showed a statistically significant rise in LH and FSH at 30 and 60 min. The LH level rose from 6.67 ± 1.53 mIU/mL (±SD) at baseline to 21.61 ± 7.19 mIU/mL at 30 min ($P < 0.001$) and 19.50 ± 6.62 mIU/mL at 60 min ($P < 0.001$) after stimulation. The FSH level rose from 3.22 ± 1.40 mIU/mL (±SD) at baseline to 7.61 ± 3.31 mIU/mL at 30 min ($P < 0.001$) and 7.50 ± 3.13 mIU/mL at 60 min ($P < 0.001$) after stimulation (significance determined by analysis of variance with repeated measures).

TABLE 1. Demographic data on men with sexual dysfunction

Case, age (yr)	Duration (yr)	Type of impotence	Testes (cm)	Stress	Alcohol	Medications	Medical diagnosis
1,61	1.75	Gradual, partial	4.0 × 3.0	0	0–1+	Dipyridamole; diltiazem; aspirin	S/P carcinoma of sigmoid; S/P hip arthroplasty; coronary artery disease; S/P myocardial infarction
2,64	4.5	Gradual, partial	3.5 × 2/5	0	0–1+	Lovastatin	Hyperlipidemia; borderline hypertension
3,71	4.0	Progressive, total	4.5 × 3.5	0	0	Insulin	Type II diabetes mellitus; basal cell carcinoma; S/P colectomy (ulcerative colitis)
4,65	2.0	Progressive, total	4.0 × 3.0	0	2+	Enlalapril; S/P nicotine (10 yr)	Hypertension; chronic obstructive pulmonary disease
5,70	13.5	Progressive, total	4.0 × 3.0	0	0	L-T; gemfibrozil; hydrochlorothiazide; amiloride	Hyperlipidemia; hypothyroidism; hypertension
6,59	3.0	Gradual, partial	5.0 × 4.0 L 4.0 × 3.0 R varicocele	0	1+	Atenolol; lovastatin; S/P nicotine (14 yr)	Hyperlipidemia; hypertension; S/P cerebrovascular accident
7,48	5.0	Gradual, partial	4.0 × 3.0	1+ work	1+	Naproxen	Tendinitis
8,47	10.0	Relative, partial	4.0 × 3.0 L 4.5 × 3.5 R	2+ work, home	1+	S/P Nicotine (5 yr)	Duodenitis; wife, uterine carcinoma
9,68	4.0	Progressive, total	4.0 × 3.0	0	1+	Dipyridamole; lovastatin; S/P glybride	S/P Cerebrovascular accident; hyperlipidemia; type II diabetes mellitus; coronary artery disease (S/P myocardial infarction)
10,42	2.0	Intermittent, ↓ libido	5.0 × 3.5	2+ work, travel	0–1+	Theophyllin; glipizide	Asthma; type II diabetes mellitus
11,63	1.25	Gradual, partial	4.0 × 3.0 L 3.5 × 2.5 R	1+ medical	1+	Digoxin; warfarin; quinidine; furosemide; pindolol	Atrial fibrillation; ventricular tachycardia (AICD): coronary artery disease (S/P coronary artery bypass graft)
12,68	4.0	Progressive, total	5.5 × 4.0 L 5.0 × 3.5 R	0	0–1+	Glyburide; enalipril	Type II diabetes mellitus; hypertension
13,52	0.75	Gradual, partial	4.0 × 3.0 varicocele	0	1+	None	Sclerosing epithelioma; squamous cell carcinoma *in situ*
14,60	3.5	Progressive, total	5.0 × 4.0	1+ work	0	S/P nicotine (3 yr)	Type II diabetes mellitus; silent ischemia
15,60	5.0	Gradual, partial	4.0 × 3.0	0	0	Glyburide; S/P hydrochlorothiazide; allopurinol	Type II diabetes mellitus; hypertension; hyperuricemia
16,56	0.5	Partial, ↓ libido	4.5 × 3.5 Peyronie's disease	1+ financial	0	S/P nicotine (6 yr); nifedipine; diltiazem	S/P carotid stenosis; coronary artery disease (angina)
17,68	10.0	Partial, ↓ libido	3.0 × 2.5	2+ marital	0–1+	Aspirin	Borderline hypertension; osteoarthritis

S/P, Status post; AICD, automatic implantable cardioverter defibrillator.

TABLE 2. Baseline hormones in men with sexual dysfunction

Case no.	Total testosterone (>250 ng/dL)	Free testosterone (<50 yr old, >16 pg/mL; >50 yr old, >11 pg/mL)	LH (<13 mIU/mL)	FSH (<7 mIU/mL)	PRL (<15 ng/mL)	Estradiol (<35 pg/mL)	Sex hormone binding globulin (0.2–1.4 μcg DHT bound/dL)
1	220	10.4	5	3	2	17	0.6
2	215	9.5	4	2	4	24	0.9
3	210	9.7	6	2	2	8	1.0
4	251	11.2	4	1	3	8	1.4
5	252	10.8	6	6	2	10	0.8
6	258	8.9	6	3	2	34	1.2
7	274	15.7	7	2	4	30	0.6
8	272	12.5	6	4	3	20	0.7
9	256	8.6	7	3	2	33	1.0
10	272	14.3	7	3	2	17	0.6
11	198	8.2	7	5	3	18	1.15
12	146	5.4	7	3	2	17	1.4
13	215	8.2	9	2	4	27	1.13
14	275	9.9	7	4	4	17	1.4
15	263	9.5	10	5	6	26	0.52
16	275	11.4	5	4	4	13	1.0
17	253	10.0	6	4	4	18	1.24

Clomiphene challenge test

The integrity of the entire hypothalamic-pituitary-testicular axis was tested with the clomiphene challenge test and showed a significant response. LH rose from 6.41 ± 1.50 mIU/mL on day 0 to 9.23 ± 2.75 mIU/mL on day 7 ($P < 0.001$) and 9.71 ± 2.69 mIU/mL on day 10 ($P < 0.001$) after stimulation. FSH rose from 3.06 ± 1.09 mIU/mL on day 0 to 5.06 ± 2.46 mIU/mL on day 7 ($P < 0.001$) and to 5.82 ± 2.67 mIU/mL on day 10 ($P < 0.001$) after stimulation (significance determined by analysis of variance with repeated measures). Total testosterone rose from 262.2 ± 75.8 ng/dL on day 0 to 389.2 ± 94.9 ng/dL on day 7 ($P < 0.001$) to 480.7 ± 129.7 ng/dL on day 10 ($P < 0.001$) after stimulation (analysis of variance with repeated measures). The free testosterone level rose from 10.0 ± 2.5 pg/mL on day 0 to 13.9 ± 3.9 pg/mL on day 7 ($P < 0.001$) to 16.3 ± 3.8 pg/mL on day 10 ($P < 0.001$) after stimulation (significance determined by analysis of variance with repeated measures).

Treatment phase

The treatment phase showed a significant response for clomiphene over the placebo as well as over the baseline. This was true for all hormones tested after both the first and second months of therapy (Fig. 1). Also, the values for all hormones did not significantly differ between the first and second months of therapy. The serum level of LH rose from 6.4 ± 1.5 to 10.3 ± 3.5 mIU/mL (±SD) at 1 month and 10.2 ± 3.1 mIU/mL at 2 months ($P < 0.01$). The level of serum FSH likewise rose from 3.4 ± 1.4 to 5.6 ± 2.7 mIU/mL at 1 month

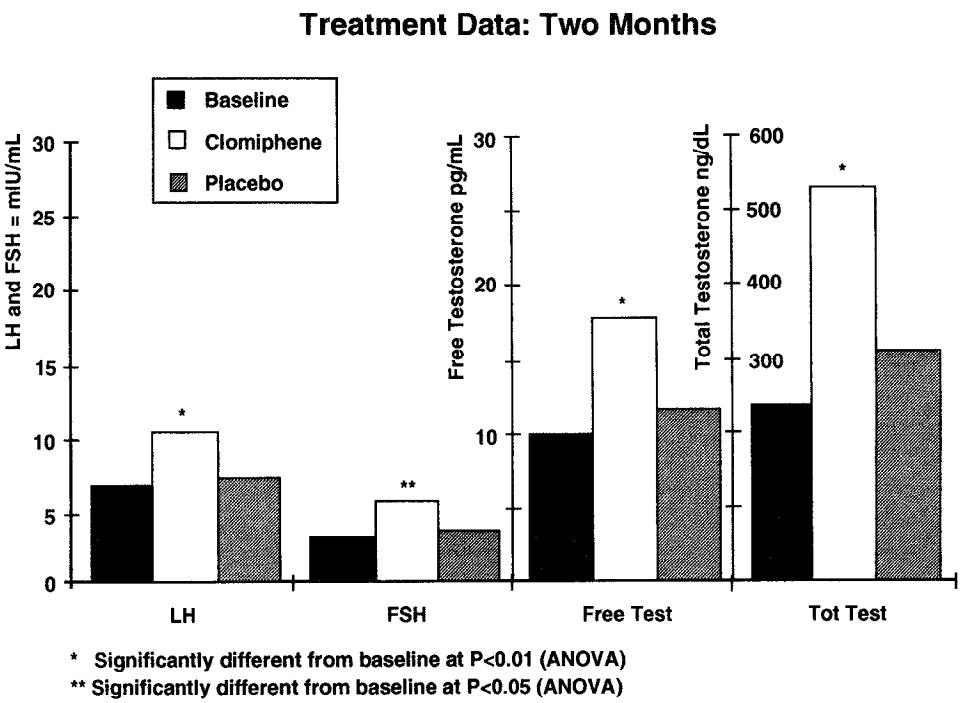

FIG. 1. Hormone levels after 2 months of treatment with either placebo tablets or clomiphene citrate (50 mg, orally) on Monday, Wednesday, and Friday.

TABLE 3. Questionnaire data

Parameter	Baseline	Clomiphene citrate	Placebo	*P* value
Sexual satisfaction index	7.9 ± 3.3	8.8 ± 2.7	8.6 ± 1.9	NS
Global sexual satisfaction index	1.6 ± 1.3	1.6 ± 1.9	1.9 ± 1.7	NS
Kiss (monthly)	4.3 ± 2.7	3.5 ± 2.2	4.0 ± 2.6	NS
Masturbation (monthly)	2.4 ± 1.7	1.8 ± 1.3	2.5 ± 1.8	NS
Intercourse (monthly)	1.9 ± 1.4	2.0 ± 1.4	2.1 ± 1.3	NS
Actual/ideal ratio	0.46 ± 0.35	0.43 ± 0.31	0.44 ± 0.28	NS
Fantasy (monthly)	3.2 ± 2.0	2.8 ± 1.8	3.4 ± 2.2	NS

Values are the mean ± SD.

TABLE 4. Nocturnal tumescence parameters

Parameter	Baseline	Clomiphene citrate	Placebo	*P* value
Total area				
Tip rigidity/h slept, maximum	494.1 ± 710.8	417.4 ± 531.3	301.8 ± 413.1	NS
Average rigidity, tip	15.1 ± 14.1	15.8 ± 19.8	15.2 ± 15.8	NS
Total area base				
Tumescence/h slept, maximum	124.2 ± 95.8	142.9 ± 90.1	94.5 ± 73.2	NS
Average tumescence base	7.6 ± 2.9	7.0 ± 3.4	7.6 ± 2.9	NS
Change in tumescence base	17.8 ± 7.4	19.1 ± 7.5	16.5 ± 7.2	NS

Values are the mean ± SD.

and was at 5.6 ± 3.4 mIU/mL at 2 months ($P < 0.05$). The level of serum total testosterone was also significant, rising from 237.6 ± 38.3 to 549.6 ± 131.9 ng/dL at 1 month and to 527.0 ± 149.9 ng/dL at 2 months ($P < 0.01$). The level of serum free testosterone rose in parallel from 10.0 ± 2.5 to 19.2 ± 3.9 pg/mL at 1 month and 17.8 ± 5.0 pg/mL at 2 months ($P < 0.01$).

Questionnaires and nocturnal monitoring

The responses to questionnaires (Table 3) revealed no significant changes in a variety of parameters related to sexual function as viewed subjectively by the patient. χ^2 analysis of the patients' response, when they were asked whether they thought that drug A or drug B was the active drug, confirmed that the subjects were not able to distinguish correctly. Objective monitoring of nocturnal tumescence and rigidity with the RigiScan also did not show any significant change during any phase of treatment (Table 4).

Secondary analysis

In secondary analysis of the data, when the patients were separated by the median age of the sample, the mean ages of the two groups were 53.0 yr (n = 8) and 66.4 yr (n = 9). Isolated parameters were found that seemed to improve with higher testosterone levels in the younger group. This was true of both nocturnal penile tumescence and rigidity testing as well as from the results of the questionnaires (Table 5).

In a further secondary analysis, the patient population was separated by men with (n = 9) or without (n = 8) diabetes, hypertension, or both (Table 6). There was no significant age difference, nor was there any difference in the basal hormone levels. The men without diabetes and hypertension showed some limited significant sexual improvement in both objective and subjective measurements. The stimulated total testosterone level was not different in the two groups, but the free testosterone level showed a trend toward significance in men without diabetes or hypertension.

TABLE 5. Objective and subjective sexual responses in the patient population separated into younger and older groups during the treatment phase with clomiphene citrate

	Younger	Older	*P* value
No.	8	9	
Mean age (yr)	53.0	66.4	
Baseline total testosterone[a]	263 ± 20	222 ± 36	<0.013[b]
Stimulated total testosterone[a]	489 ± 150	577 ± 145	NS
Baseline free testosterone[a]	10.3 ± 2.7	9.3 ± 1.8	NS
Stimulated free testosterone[a]	17.9 ± 5.6	18.8 ± 4.0	NS
Average tip rigidity[a]	25.9 ± 23.6	6.6 ± 10.2	<0.003[c]
Change base tumescence[a]	21.6 ± 8.05	16.8 ± 6.7	<0.040[c]
Average base tumescence[a]	7.8 ± 3.2	6.3 ± 3.7	<0.059[c]
Sexual satisfaction index[a]	10.0 ± 0.6	7.5 ± 3.6	<0.032[c]
Intercourse	2.7 ± 1.6	1.2 ± 0.4	<0.029[c]
Actual *vs.* ideal	0.6 ± 0.4	0.3 ± 0.1	<0.066[c]

[a] Mean ± SD.
[b] By two-tailed *t* test.
[c] By two-way analysis of variance; significance is consistent across treatment *vs.* placebo groups.

Discussion

Sexual function declines with age, and, as noted by Martin (16), even in healthy men with several partners, the frequency of sexual intercourse declined to nearly nonexistent levels in a large number of men more than 65 yr old. On a similar note, but in a less permissive society, Kinsey and colleagues (17) provided a reason for this decline when they reported an increasing prevalence of impotence with advancing age (<2% until age 40 yr, 6.7% by age 55 yr, and increasing to 24% by age 70 yr). Recently, the community-based random sample of noninstitutionalized men provided similar data, reporting that the prevalence of total impotence tripled from 5% to 15% between 40 and 70 yr of age. More recently, it was thought that as many as 52% of men more than 40 yr of age had some degree of sexual difficulty (18).

A slow but steady decline in the level of circulating androgens is known to occur in aging men. Declining levels of total testosterone (19), free testosterone (4), and bioavailable testosterone (20) have suggested decreasing testicular func-

TABLE 6. Separation of patient population by medical condition, *i.e.* those with and without diabetes or hypertension or both, during the treatment phase with clomiphene citrate

	Without diabetes mellitus/hypertension	With diabetes mellitus/hypertension	*P* value
No.[a]	8	9	
Mean age (yr)	62.6	57.4	NS[b]
Baseline total testosterone[c]	240 ± 37	242 ± 41	NS[b]
Stimulated total testosterone[c]	541 ± 147	531 ± 160	NS[b]
Baseline free testosterone[c]	10.7 ± 2.5	9.8 ± 2.4	NS[b]
Stimulated free testosterone[c]	20.1 ± 5.4	16.3 ± 4.0	<0.11 (NS[b] 0)
Average tip rigidity[c]	21.8 ± 20.7	10.4 ± 18.4	<0.017[d]
Change base tumescence[c]	21.0 ± 8.1	17.3 ± 6.9	<0.006[d]
Masturbation[c]	2.2 ± 1.6	1.3 ± 0.8	<0.006[d]
Global sexual satisfaction index	2.8 ± 2.4	0.86 ± 1.07	<0.018[d]

[a] Two patients had both diabetes and hypertension.
[b] By two-tailed *t* test.
[c] Mean ± SD.
[d] By Two-way analysis of variance; significance is consistent across treatment *vs.* placebo groups.

tion. Rising gonadotropin levels (21, 22), altered gonadotropin rhythm impulses (23–25), and lowered bioavailable/immunoassay ratios of gonadotropins (26) have supported the impact of aging on the hypothalamic-pituitary axis, suggesting that age in men affects the entire hypothalamic-gonadotropin-Leydig cell axis (27).

Armed with the facts of hypogonadism and decrease in sexual activity and with the prior knowledge that sexual behavior and libido are affected by circulating androgens (28–30), causality to the declining androgens for decreased sexual function was assigned by association (16). Closer examination of the relationship between hypogonadism and impotence suggested that although hypogonadism and impotence are commonly associated, they may be independent problems associated with aging (12).

The conclusion found support when reduced androgen levels were restored by exogenously administered testosterone but did not seem to restore sexual capabilities (9, 10, 28). Despite this evidence, testosterone replacement in older men is practiced routinely when a decline in sexual function is reported. These practices found support in the lay literature and may expose elderly men to prostate stimulation and other potentially undesired effects (13).

Secondary hypogonadism, as defined in our patients, refers to a low free testosterone level that is not compensated for by an increase in LH secretion. Our work, reported in this article, helps to nullify the idea of using testosterone indiscriminately in an aging population with the explicit purpose of restoring sexual function. Whereas previous attempts to use exogenous testosterone did not help, we have shown that elevated endogenous testosterone levels did not fare any better. To assess subjective sexual performance, we questioned the patients by using focused questionnaires. To judge objective sexual capability, we used nocturnal penile tumescence and rigidity monitoring and, instead of using exogenous testosterone, which can suppress the hypothalamic-pituitary axis, we used clomiphene citrate in a population of 17 impotent men with secondary hypogonadism. Clomiphene citrate, as we (14) reported previously in this type of population, elevates circulating androgen levels by stimulating the Leydig cells indirectly by means of stimulating GnRH production from the hypothalamus. Despite the significant rise in androgen levels over a moderate period of time (2 months), no clear improvement occurred in the subjects' self-reported sexual behavior or their objective nocturnal penile tumescence and rigidity measurements. Questioning the patients in the office at each stage of the double blind, placebo-controlled trial revealed that the patients were unable to distinguish between the active and inactive drug.

If, however, our treatment group was divided by the median age of the population, the younger men's responses became significant compared with those of the older men. The same was somewhat true when the responses of men without hypertension or diabetes were compared with those of men who had these conditions. Although the small numbers of men prevent sweeping conclusions, further studies would seem warranted. Supporting our observations, Gray *et al.* (31) and Handelsman (32) also showed that older men with ill health had lower testosterone levels than their healthy age-matched counterparts. Lower free testosterone levels were shown in men with hypertension when they were taking several different antihypertensive medications (32, 33). It is also possible, and probable, that many conditions, especially diabetes and hypertension, cause erectile dysfunction without any effect on the hormone levels, because of direct neural and vascular damage.

In certain circumstances, especially in younger patients and those who do not manifest one or more chronic diseases, *i.e.*, diabetes and hypertension, a short course of clomiphene citrate may be tried for several months when the free testosterone level is seen to be lowered. It must also be remembered that 16% of our initial study group, who also had slightly low free testosterone levels, had completely normal results on nocturnal penile tumescence testing consistent with psychological impotence. Thus, the baseline status of the patient must be ascertained accurately either by history or nocturnal tumescence testing.

Although certain selected patients may respond to hormonal augmentation, the clear message seems to be that sexual dysfunction and associated low testosterone levels are not causally related in all patients and that androgens should not be given indiscriminately to every man over a predetermined age.

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