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Outcomes of Long-Term Testosterone Replacement in Older Hypogonadal Males: A Retrospective Analysis

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ABSTRACT

To determine the complications, toxicities, and compliance of long term testosterone replacement in hypogonadal males, we retrospectively assessed 45 elderly hypogonadal men receiving testosterone replacement therapy and 27 hypogonadal men taking testosterone. Hypogonadism was defined as a bioavailable testosterone serum concentration of 72 ng/dL or less. Both groups received baseline physical examinations and blood tests. The testosterone-treated group received 200 mg testosterone enanthate or cypionate im every 2 weeks, and follow-up examinations and blood samplings were performed every 3 months. The control group had a single follow-up blood test and physical examination.

There was no significant difference in the initial blood tests in the two groups. At 2 yr follow-up, only the hematocrit showed a statistically significant increase in the testosterone-treated group compared to the control group ($P < 0.001$). A decrease in the urea nitrogen to creatinine ratio and an increase in the prostate-specific antigen concentration was not statistically significant. Eleven (24%) of the testosterone-treated subjects developed polycythemia sufficient to require phlebotomy or the temporary withholding of testosterone, one third of which occurred less than 1 yr after starting testosterone treatment. There was no significant difference in the incidence of new illness in the two groups during the 2-yr follow-up. Alhough self-assessment of libido was dramatically improved in the testosterone-treated group ($P < 0.0001$), approximately one third of the subjects discontinued therapy.

In conclusion, testosterone replacement therapy appears to be well tolerated by over 84% of the subjects. Long term testosterone replacement to date appears to be a safe and effective means of treating hypogonadal elderly males, provided that frequent follow-up blood tests and examinations are performed. (*J Clin Endocrinol Metab* **82**: 3793–3796, 1997)

MUCH CONTROVERSY exists concerning the role of testosterone replacement therapy in the hypogonadal elderly male. Serum testosterone levels decline steadily after the age of 50 yr, and estimations are that by the age of 70 yr, the testosterone production rate is approximately two thirds that of a healthy male under 50 yr old, and by 80 yr of age, the production rate decreases to less than 50% that of a younger male (1–7). The decline in bioavailable testosterone may be partially responsible for the frailty syndrome (8–10) seen in the aging male, which includes accelerated osteoporosis, decreased muscle mass, and anemia. These symptoms may also be accompanied by hot flashes, mood disturbances, and fatigue, not dissimilar to menopause in women. The symptoms, however, are generally minimal or may even go unnoticed, as the decline in testosterone occurs over many years rather than abruptly as with estrogen in women. Although it was originally believed that the type of hypogonadism seen in older men was due to primary testicular dysfunction (primary hypogonadism), it has now become apparent that failure of the hypothalamic-pituitary function (secondary hypogonadism) is much more common than initially thought (4, 11–15). Secondary hypogonadism, as evidenced by a low testosterone and bioavailable testosterone and a low or low normal LH concentration, seems to be the rule rather than the exception with aging. However, the age-related decline in testicular Leydig cells (16) make primary hypogonadism a relatively common occurrence in the very old, and it is likely that both primary and secondary hypogonadism, to varying degrees, are responsible for the decline in testosterone levels seen with advancing age. Whatever the mechanism of hypogonadism, testosterone replacement has been gaining popularity among clinicians for alleviating symptoms and signs of hypogonadism in old age. Although the immediate effects of exogenous testosterone have been demonstrated (17–23), data concerning the long term benefits, side-effects, and toxicity of supplemental testosterone in older males remain limited and incomplete (24, 25). This study was undertaken to assess the safety of long term testosterone supplementation in the hypogonadal elderly male, particularly the effect on clinical and hematological parameters, as well as compliance of the subjects receiving testosterone.

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Subjects and Methods

Subjects for this study were derived from over 200 participants of the sexual dysfunction clinic at St. Louis University Health Sciences Center. All hypogonadal males were eligible. Hypogonadism was defined as having a serum bioavailable (free plus weakly bound) testosterone level of 72 ng/dL or less. This cut-off point was previously established as a value not seen in eugonadal young males on the basis of statistical analysis of a large number of healthy young males (4, 5, 11). Hypogonadal males receiving testosterone injections formed the study group, whereas the control group consisted of those who chose not to receive such therapy. All subjects underwent an initial assessment. This included a baseline history of medical illnesses, physical examination, and blood tests. The 45 subjects in the study group received testosterone enanthate or cypionate (200 mg, im, every 2 weeks) and follow-up blood sampling every 3 months. These 2 testosterone preparations have similar

pharmacokinetics (26, 27). The 27 subjects in the control group had a single follow-up interview and blood test at various times after the initial assessment. The blood tests included electrolytes, urea nitrogen, creatinine, hemoglobin, hematocrit, liver profile, cholesterol, albumin, and prostate-specific antigen. In addition, baseline blood tests included FSH, LH, PRL, thyroid function tests, and TSH. To ensure concordance between the two groups, baseline data were compared (Table 1). Benign prostatic hypertrophy was assessed by digital rectal examination and subjective evaluation using the criteria of the American Urologic Association symptom index (28). Similarly, peripheral vascular disease, angina, and transient ischemic attacks were assessed by inquiring about the appropriate symptom. The occurrence of new illness during the course of the study was compared in the 2 groups using Fisher's exact test, as was the follow-up of the subjective rating of libido compared to the initial presentation. Subjects were asked to categorize their libido as being the same, better, or worse. Furthermore, changes between baseline and 2 yr follow-up values of the hematological tests in the testosterone-treated group were compared to those in the control group using Student's *t* test.

Results

Seventy-two subjects were studied in total, with 27 in the control group and 45 in the testosterone-treated group. The mean bioavailable testosterone levels were 42.49 ± 2.90 and 40.11 ± 3.49 ng/dL in the testosterone and control groups, respectively. This difference was not statistically significant. The 2 groups similarly showed no statistically significant difference in baseline hematological studies (Table 1). The control group had follow-up blood sampling performed at 1 yr in 4 subjects (15%), at 2 yr in 15 subjects (55%), or at 3 yr or more in the remaining 8 subjects (30%). Of the 45 subjects in the study group, 31 (67%) had been receiving testosterone injections for at least 1 yr, 26 (58%) subjects had been receiving testosterone for at least 2 yr, and 15 (33%) subjects had been receiving testosterone for 3 yr or more.

The 2 yr changes in serum and hematocrit values of the two groups are compared in Table 2. There were no significant differences in the prostate-specific antigen concentration. The urea nitrogen to creatinine ratio dropped in the study group, but the change was not statistically significant. Only hematocrit showed a significant increase in the testosterone-treated group compared to that in controls. Eleven subjects (24%) in the testosterone group developed polycythemia (hemoglobin, >17 g/dL; hematocrit, >52%), warranting temporary withdrawal of testosterone therapy or phlebotomy. Of these, the first occurrence of polycythemia was within the first year of therapy in six (33%) subjects, between 1–2 yr in 3 (6.7%) subjects, and beyond 2 yr in two (4.4%) subjects.

Comparison of self-assessment of libido at the 2 yr point showed a dramatic improvement in the testosterone group compared to that in the controls (Fig. 1). The incidence of new illnesses during the course of the study was not significantly different in the two groups for coronary artery disease, peripheral vascular disease, myocardial infarctions, angina, diabetes mellitus, or transient ischemic attacks (Table 3). Benign prostatic hypertrophy (BPH) has long been a concern associated with long term testosterone administration. This study found that the control group had a higher rate of BPH than the study group, but the difference was not statistically significant.

Two deaths occurred in each group due to myocardial infarction and lung cancer in the control group, and colon cancer and stroke in the study group. Although the death rate in the testosterone group was less than that in the control group, the difference was not statistically significant. A total of 14 (31.1%) subjects discontinued therapy or were lost to follow-up. Of these, 8 (17.8%) occurred during the first year of treatment, 3 (6.7%) between 1–2 yr of therapy, and 3 (6.7%) occurred beyond 2 yr of therapy (Table 4). Reasons for discontinuing testosterone are given in Table 5.

TABLE 1. Mean baseline blood tests in the study and control groups

	Control (n = 27)	Study (n = 31)
Age (yr)	69.9 ± 1.9	71.8 ± 1.7
Body mass index (kg/m^2)	26.4 ± 0.9	27.4 ± 0.7
Testosterone (ng/dL)	275.5 ± 21.0	310.9 ± 20.0
Bioavailable testosterone (ng/dL)	40.1 ± 3.5	42.5 ± 2.9
LH (U/L)	11.4 ± 1.3	15.5 ± 1.8
FSH (U/L)	13.1 ± 1.8	13.5 ± 2.0
PRL (ng/mL)	5.6 ± 0.8	6.4 ± 0.8
TSH (μg/mL)	1.6 ± 0.2	1.7 ± 0.2
T (μg/dL)	7.4 ± 0.6	7.1 ± 0.4
Cholesterol (mg/dL)	211.9 ± 6.7	216.3 ± 6.8
Hemoglobin (g/dL)	14.0 ± 0.3	14.6 ± 0.2
Hematocrit (%)	41.4 ± 0.7	42.8 ± 0.6
Albumin (g/dL)	4.0 ± 0.1	4.1 ± 0.1
Sodium (mmol/L)	139.9 ± 0.4	141.9 ± 0.4
Urea nitrogen (mg/dL)	15.9 ± 1.1	15.7 ± 0.7
Creatinine (mg/dL)	1.2 ± 0.1	1.0 ± 0.1
Urea nitrogen/creatinine	13.9 ± 0.7	15.6 ± 0.8
Aspartate aminotransferase (U/L)	28.1 ± 1.5	28.0 ± 1.6
Alanine aminotransferase (U/L)	24.7 ± 1.6	26.6 ± 2.8
Alkaline phosphatase (U/L)	95.5 ± 13.1	81.1 ± 4.4
Prostate-specific antigen (mg/dL)	1.4 ± 0.3	1.3 ± 0.2

Results are the mean ± SEM. *P* values were calculated by the unpaired *t* test and were not significant in any case.

Discussion

The long term administration of testosterone in hypogonadal males was well tolerated in 69% of the participants of this study. Both testosterone-treated and control subjects were well matched at the onset of the study. The effect of testosterone on hematocrit has been documented in several small and short term studies (17–20, 22, 24, 25). This effect was confirmed in our study. There were no adverse effects of the increased hematocrit, but frequent monitoring was necessary to avoid critically elevated hematocrit levels, which occurred in one fourth of the subjects in this study. Polycythemia generally reverts to baseline after withholding testosterone therapy, although phlebotomy was occasionally necessary for a more immediate response. Whether the use of lower, more physiological, testosterone treatment regimens would result in less polycythemia has not been studied at this time. Although the mechanism involved remains uncertain, a similar effect has been noted in anephric mice. Increased hematocrit thus appears to be mediated not only by erythropoietin, and it has been postulated that testosterone may have a direct effect on bone marrow stem cells (29–32). Exogenous testosterone has been suggested, and successfully used, for the treatment of refractory anemia in males (33).

As prostate cancer has been associated with hormone-responsive growth (34), and as benign prostatic hypertrophy and declining testosterone levels both occur in the aging

TABLE 2. Changes in blood tests at 24 months in the study and control groups

	Controls (n = 15)	Study (n = 26)	*P* value
Wt (lb)	0.03 ± 2.95	0.39 ± 1.38	NS
Cholesterol (mg/dL)	−21.14 ± 8.52	−6.77 ± 13.07	NS
Albumin (g/dL)	0 ± 0.12	0.13 ± 0.05	NS
Hematocrit (%)	−0.22 ± 0.49	4.81 ± 0.76	<0.001
Alanine aminotransferase (U/L)	1.87 ± 1.83	6.74 ± 2.30	NS
Aspartate aminotransferase (U/L)	−0.33 ± 1.85	1.48 ± 1.90	NS
Urea nitrogen/creatinine	0.31 ± 0.75	−1.55 ± 1.03	NS
Prostate-specific antigen (mg/dL)	0.25 ± 0.40	0.49 ± 0.23	NS

The δ values were calculated as the 24-month value minus the baseline value. Results are the mean ± SEM.
P values were calculated by the unpaired *t* test.

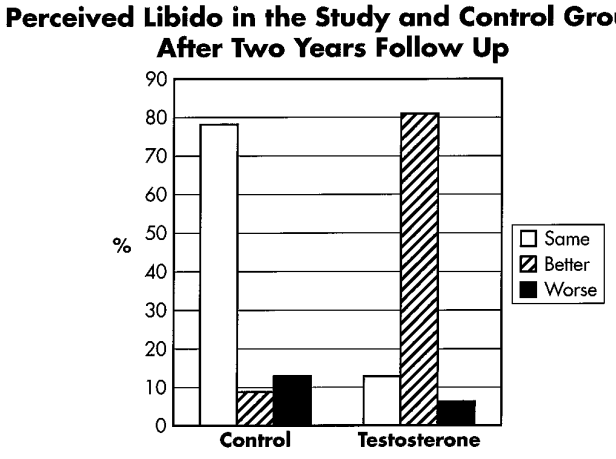

FIG. 1. Comparison of self-assessment of libido at the 2 yr point showed a dramatic improvement in the testosterone group compared to controls.

TABLE 3. Comparison of new occurrences of illnesses and deaths in the study and control group at 24 months

	Controls (n = 23)	Study (n = 26)
Angina	3	1
Myocardial infarctions	0	1
Cerebrovascular accidents	1	1
Peripheral vascular disease	0	0
Benign prostatic hypertrophy/prostate cancer	6	2
Diabetes mellitus	0	1
Deaths	2	2

P values were calculated by Fisher's exact test and were not significant in any instance.

TABLE 4. Time of discontinuation of testosterone therapy

Time of discontinuation of testosterone	No.	%
<12 months	8	17.8
12–24 months	3	6.7
>24 months	3	6.7
Total	14	31.1

TABLE 5. Reasons for discontinuing testosterone

Reason for discontinuing therapy	No.	%
No improvement	5	11.1
Gynecomastia	1	2.2
Hematoma at injection site	1	2.2
Sleep apnea	1	2.2
Inconvenience	1	2.2
Concerned about side effects	2	4.4
Lost to follow-up	3	6.7
Total	14	31

population, there has long been a concern among clinicians that chronic testosterone replacement might have an adverse effect on the prostate. Recent studies indicate that the clinical course of prostate cancer is accelerated by testosterone, but the incidence is not increased by it (17, 29). In other words, testosterone does not appear to cause prostate cancer. Although prostate carcinoma is a clear contraindication for testosterone replacement therapy, there is no clinical evidence that testosterone accelerates BPH (17, 24, 35). In fact, in this study, subjects receiving testosterone had fewer complaints of bladder outlet obstruction symptoms than those in the control group, although the difference was not statistically significant. The frequent follow-up visits in men taking testosterone, which included a rectal exam and serum prostate-specific antigen measurement, may be an effective screening mechanism that is not operative in men not taking testosterone, who may have much less frequent primary care checkups. Consequently, it is possible that should new prostate cancer occur, it may be diagnosed earlier in this group, resulting in a more favorable outcome.

The adverse effect of testosterone on the lipid profile has been documented in younger men, although the long term effect of the change on mortality and morbidity is uncertain. Although a drop in serum high density lipoprotein cholesterol of 10–15% has been shown to occur in many studies in younger men (17, 36, 37), other studies were unable to confirm a decline in high density lipoprotein cholesterol or an increase in total cholesterol in older men (18, 38, 39). The long term clinical significance is not clear, as in our experience there is no increase in angina, myocardial infarctions, or strokes in patients receiving testosterone for up to 3 yr. Furthermore, total cholesterol in the testosterone-treated group and the control group did not significantly differ in this study.

Sleep apnea, associated with testosterone, has been reported previously (40). In this study only one subject reported worsening sleep apnea, leading to discontinuation of testosterone. In general, however, most subjects who reported a favorable response to testosterone also report better sleep habits as part of their overall sensation of well-being associated with testosterone.

It is not surprising that testosterone has a minimal mineralocorticoid effect, because steroid compounds differ in quantitative, rather that absolute, qualitative effects. No significant weight gain, fluid retention, or sodium retention

were noted in this study. Short term studies have indicated a decrease in the urea nitrogen to creatinine ratio (18). This difference was not found to be significant in this study. It is possible that an early change in sodium levels and fluid shifts are overcome with the long term use of testosterone.

Conclusion

Testosterone replacement therapy was well tolerated in 69% of the subjects in this study. Approximately one third of the subjects discontinued therapy, most of which occurred soon after starting the treatment (~18% within 1 yr). The most common reason for discontinuing testosterone replacement therapy was the lack of noticeable improvement in the presenting symptom, or the inconvenience of therapy and frequent follow-up visits. Of those who continued therapy, most reported an improvement in libido, energy, mood, and sleep. The only strict contraindications for testosterone use are prostate cancer, allergic hypersensitivity to the testosterone preparation (41), or an elevated hematocrit. In the absence of these, long term testosterone replacement therapy to date appears to be safe and effective. Frequent follow-up visits and blood testing (hematocrit and prostate-specific antigen) are essential, however, for proper management of the hypogonadal older male.

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