Long-Term Testosterone Therapy Improves Urinary and Sexual Function, and Quality of Life in Men with Hypogonadism: Results from a Propensity Matched Subgroup of a Controlled Registry Study

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Purpose: We investigated the effects of long-term testosterone therapy on urinary and sexual function, and quality of life in hypogonadal men.

Materials and Methods: We performed an observational, prospective, cumulative registry study in 656 men with a mean ± SD age of 60.7 ± 7.2 years who had total testosterone 12.1 nmol/l or less and symptoms of hypogonadism. In the testosterone treated group 360 men received parenteral testosterone undecanoate 1,000 mg/12 weeks for up to 10 years. The 296 men who elected against testosterone therapy served as controls. From each group 82 patients were propensity matched by age, waist circumference and body mass index, resulting in 82 matched pairs of 164 men. Data were analyzed and estimated differences between the groups were adjusted for components of metabolic syndrome and quality of life.

Results: We found significant decreases in I-PSS (International Prostate Symptom Score) and post-void bladder volume (each $p < 0.0001$) in patients receiving testosterone therapy but not in the untreated group. We recorded a decrease in AMS (Aging Males' Symptoms Scale) in the testosterone treated group but not in the untreated group ($p < 0.0001$). We also recorded significant improvement in the IIEF-EF (International Index of Erectile Function-Erectile Function) domain in the testosterone treated group but not in the untreated group ($p < 0.0001$). The improvement was maintained throughout followup.

Conclusions: Long-term testosterone therapy in hypogonadal men resulted in significant improvements in urinary and sexual function, and in quality of life. In untreated hypogonadal men voiding and erectile function deteriorated with continued followup.

Key Words: testis, testosterone, erectile dysfunction, lower urinary tract symptoms, quality of life

Abbreviations and Acronyms

AMS = Aging Males' Symptoms Scale
BMI = body mass index
BPH = benign prostatic hyperplasia
ED = erectile dysfunction
EF = erectile function
HDL = high density lipoprotein
IIEF = International Index of Erectile Function
I-PSS = International Prostate Symptom Score
LDL = low density lipoprotein
LUTS = lower urinary tract symptoms
PSA = prostate specific antigen
QoL = quality of life
T = testosterone

TESTOSTERONE deficiency (hypogonadism) contributes to a host of pathophysiological conditions which negatively impact metabolic and sexual function, as well as overall health and QoL.[1] T deficiency is also associated with obesity, metabolic syndrome, reduced libido and increased ED, and orgasmic dysfunction. T therapy in men with T deficiency improves cardiometabolic and sexual function.[2,3]

Haider et al suggested that LUTS are in part attributable to reduced T levels.[4] A systematic review of the

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literature did not provide evidence that T therapy worsens LUTS or increases prostate volume in men with T deficiency.[5] Francomano et al also reported that in obese men with hypogonadism and metabolic syndrome LUTS were improved in those treated vs untreated with T.[6]

Although significant improvements in voiding symptoms or LUTS following T therapy were reported in some studies,[7,8] a recent systematic review suggested a lack of consistent effects of T therapy on LUTS.[9] Crawford et al found that endogenous T levels did not correlate with LUTS or prostate size[10] and these findings support the saturation theory.[11] This is consistent with data reported by Schatzl et al, in which T levels were shown to have no impact on LUTS status or prostate volume.[12] On the other hand, in a recent review Baas and Köhler suggested that T may be beneficial for BPH/LUTS, likely via increased expression and activity of nitric oxide synthase concomitant with smooth muscle relaxation.[13] Concern remains that T therapy may worsen LUTS secondary to BPH, although few major adverse events have been reported with T treatment.

We examined the effects of long-term T therapy in men with T deficiency on urinary and erectile function, and compared the findings with those of men in the same registry who remained untreated. More importantly we performed propensity matching analysis[2] to adjust for a number of variables to ensure that confounding factors such as age and obesity were considered. This was done to assess changes in urinary and sexual function as well as in QoL. The currently reported data and those reported previously[2] were derived from the same registry.

PATIENTS AND METHODS

We performed an observational, prospective, cumulative registry study in 656 men with a mean ± SD age of 60.72 ± 7.15 years, total T 12.1 nmol/l or less and hypogonadism symptoms. This study followed the ethical guidelines formulated by the German Ärztekammer (Medical Association) for observational studies in patients receiving standard treatment. After obtaining information on the nature and purpose of the study subjects who consented were included in the registry and their data were analyzed. Men seeking medical treatment for urological complaints were enrolled. In the T treated group 360 men received parenteral T undecanoate 1,000 mg/12 weeks after an initial 6-week interval for up to 10 years. The 296 men who had elected not to receive T therapy served as controls. Median followup in the 2 groups was 8 years.

Assessment and Followup

We measured certain parameters, including total T, patient weight, waist circumference, BMI, hematocrit, fasting glucose, HbA1c, systolic and diastolic blood pressure, heart rate, pulse pressure, rate pressure product, lipid profile (total, LDL and HDL cholesterol, and triglycerides), C-reactive protein, liver transaminases and prostate specific antigen, as described previously.[2,4] We also assessed prostate volume using the Sonoace SA 8000 SE ultrasound device (Medison, Petach Tikva, Israel) with ultrasound probes. Patients completed the I-PSS, AMS and IIEF-EF questionnaires. Measures were taken 2 to 4 times per year and the annual average was calculated. Measurements were made as previously described.[2]

Statistical Methods

In the treated group patients returned quarterly for T injections while in the control group patients returned biannually for routine visits. Data on the 2 groups were averaged across each year of patient participation in the study. The obtained yearly data were used to assess differences between the 2 groups while adjusting for possible confounding variables.

Adjusted multivariable analyses as well as propensity score matching were done to compare the 2 groups across time while adjusting for baseline differences as described previously[2] using SAS®, version 9.3 software.

RESULTS

Baseline Characteristics of Men in Registry and 2 Propensity Matched Groups

The overall baseline characteristics of the patients included in this registry were recently reported.[2] The table lists key parameters of the overall control and T treated groups as well as the propensity matched groups. Mean baseline age of the 296 men in the untreated group was 64.8 ± 4.3 years and mean followup was 6.5 ± 1.2 years (median 7). In the T treated group of 360 men mean baseline age was 57.4 ± 7.3 years and mean followup was 6.5 ± 2.4 years (median 7).

We used propensity matching analysis to account for differences in baseline characteristics between the groups[2] and identified 82 men per group (see table). We emphasize that the 2 groups were compared in terms of changes from baseline rather than in absolute values. This was done in part to ensure that differences among the 2 groups at baseline would not contribute to the observed differences between the groups. The data presented reflect the estimated adjusted mean difference between the 2 groups. In the propensity matched groups at baseline post-void volume and IIEF in the untreated and T treated groups did not significantly differ (see table). Mean I-PSS was 7.4 ± 4.2 in the T treated group vs 4.3 ± 2.3 in the untreated group.

Total Serum Testosterone Profile in Treated and Untreated Groups

T treatment of men with T deficiency restored total T levels to within the physiological range of approximately 500 ng/dl during year 1. These levels

Baseline characteristics and concomitant medication at baseline, and major adverse events during observation in total group and propensity matched group

	Total Group			Matched Group		
	Treated	Control	p Value	Treated	Control	p Value
No. pts	360	296	—	82	82	—
Mean ± SD baseline age (yrs)	57.4 ± 7.3	64.8 ± 4.3	<0.0001	61.7 ± 5.1	61.6 ± 2.9	Not significant
Mean ± SD followup/median (yrs)	6.1 ± 2.3/7	6.2 ± 1.1/7	Not significant	7.0 ± 2.6/8	6.4 ± 1.3/7	Not significant
Mean BMI (kg/m^2)	33.1 ± 5.4	29.3 ± 3.5	<0.0001	30.7 ± 4.9	30.5 ± 3.3	Not significant
Mean ± SD urinary function:						
Post-void residual vol (ml)	47.3 ± 22.8	48.3 ± 16.3	Not significant	50.6 ± 23.6	45.7 ± 16.4	Not significant
I-PSS	6.4 ± 4	4.5 ± 2.0	<0.005	7.4 ± 4.2	4.3 ± 2.3	<0.0001
Mean ± SD IIEF-EF sexual function	19.5 ± 5	20.5 ± 3.1	<0.0001	19.5 ± 5.6	20.2 ± 3.3	Not significant
Mean ± SD prostate:						
Vol (ml)	29.2 ± 10.4	34.5 ± 5.9	<0.0001	31.4 ± 12	33.4 ± 6.2	Not significant
PSA (ng/ml)	1.74 ± 0.93	2.25 ± 1.34	<0.0001	1.95 ± 0.92	2.05 ± 1.23	Not significant
No. baseline concomitant medication (%):						
α1-Blocker	126 (35)	118 (39.9)	Not significant	34 (41.5)	25 (30.5)	Not significant
5α-Reductase inhibitor	3 (0.8)	54 (18.2)	<0.0001	2 (2.4)	5 (6.1)	Not significant
Phosphodiesterase-5 inhibitor	203 (56.4)	102 (34.5)	<0.0001	44 (53.7)	22 (26.8)	<0.0001
Phosphodiesterase-5 inhibitor cessation*	181 (89.2)	13 (12.7)	<0.0001	34 (77.3)	2 (9.1)	<0.0001
Mean ± SD AMS QoL	50.9 ± 10.3	41.0 ± 5.5	<0.0001	53.8 ± 10.6	40.6 ± 6.3	<0.0001
No. major adverse events (%):						
Death	2 (0.6)	21 (7.1)	<0.001	0	5 (6.1)	Not significant
Myocardial infarction	0	26 (8.8)	<0.001	0	9 (11)	0.003
Stroke	0	30 (10.1)	<0.001	0	7 (8.5)	0.014
Prostate Ca	7 (1.9)	12 (4.1)	0.159	4 (4.9)	3 (3.7)	0.99

* Last prescription within 36 months.

remained in the physiological range during the 8 years of followup (fig. 1). In contrast, in the untreated group mean T levels remained below 300 ng/dl throughout followup.

Testosterone Therapy Effects

Lower Urinary Tract Symptoms. A marked, progressive, sustained and significant reduction in I-PSS was recorded in men treated with T (fig. 2, *A*). The decrease in I-PSS was steep during the first 2 years. In contrast, in the untreated group I-PSS gradually increased during the same followup (fig. 2, *A*). I-PSS data were further analyzed and differences between the groups were estimated after adjustments for baseline age, weight, waist circumference, fasting blood glucose, blood pressure, lipids and AMS (fig. 2, *B*). Significant differences in adjusted I-PSS were observed throughout followup (fig. 2, *B*).

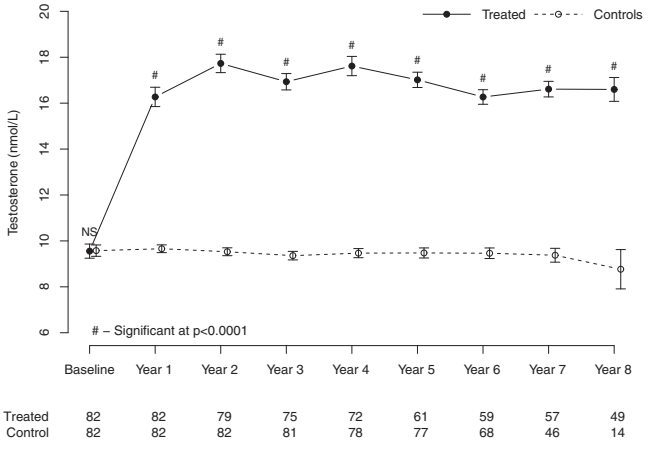

Figure 1. Testosterone levels in propensity matched, T treated and untreated groups during 8-year followup. *NS*, not significant.

At baseline 50% of the patients in the T treated group had mild symptoms (I-PSS score 0 to 7) and 50% had moderate symptoms (I-PSS 8 to 19). In the control group 91.5% of the men had mild symptoms and 8.5% had moderate symptoms, indicating that controls were in a better situation at baseline. At the last visit all patients in the T group had improved to the mild category. In the control group 61% of the men had mild symptoms and 39% had moderate symptoms at the last visit.

Post-Void Residual Bladder Volume. Figure 3 shows the progressive and significant reduction in post-void bladder volume observed in men treated with T. The decrease in post-void bladder volume was parallel to that of I-PSS. In contrast, in the untreated group post-void bladder volume gradually increased during the same followup (fig. 3).

Erectile Dysfunction. Figure 4 shows significant improvement in erectile function in response to T therapy demonstrated by the significant increase in IIEF-EF domain scores. Note that in the untreated group a progressive decrease in IIEF-EF domain scores was observed with time.

In the T treated group 17.1% of patients had no ED (IIEF-EF score 26 to 30), 30.5% had mild ED (22 to 25), 20.7% mild to moderate ED (17 to 21), 25.6% moderate ED (11 to 16) and 6.1% had severe ED

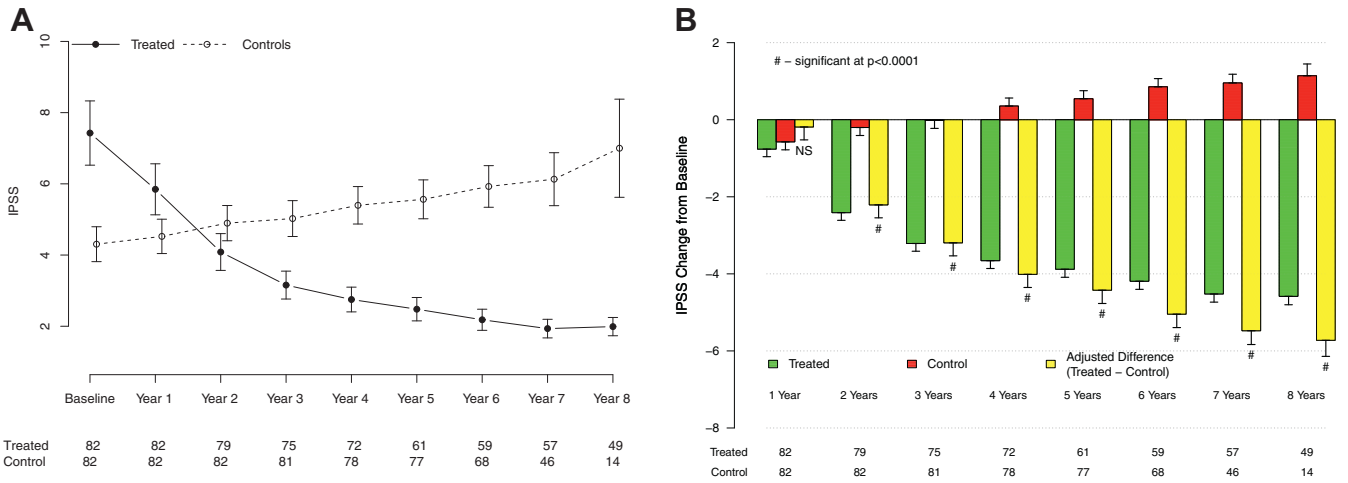

Figure 2. I-PSS. *A*, in propensity matched, T treated and untreated groups during 8-year followup. *B*, changes in T treated and untreated matched groups, and estimated differences between groups adjusted for baseline age, waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL, LDL, triglycerides and AMS.

(6 to 10). No patient had very severe ED (IIEF-EF score 0 to 5). At the last visit 74.4% of the patients had no ED, 17.1% had mild ED, 7.3% had mild to moderate ED and 1 (1.2%) had moderate ED. No patient had severe or very severe ED. In the control group 1 patient (1.2%) had no ED, 31.7% had mild ED, 52.4% had mild to moderate ED and 14.6% had moderate ED. At the last visit 51.2% of controls had moderate and 48.8% had severe ED.

Aging Male Symptom Scale Score. A significant reduction in AMS was observed in men treated with T (fig. 5, *A*). The decrease in AMS was steep during the first 2 years and then remained low throughout followup. In contrast, AMS rose slightly in the untreated group. Figure 5, *B* shows the estimated difference between the groups after adjustments for baseline age, weight, waist circumference, fasting blood glucose, blood pressure, lipids and AMS.

Prostate Volume and Prostate Specific Antigen. Mean prostate volume in the T treated group increased from 31.4 ± 12 to 33.2 ± 12.7 ml ($p < 0.0001$) while it remained stable in untreated controls (fig. 6, *A*). PSA remained unchanged in each group (fig. 6, *B* and *C*).

Adverse Events

The table shows the overall adverse events reported in this study. There were 5 deaths (6.1%), 8 nonfatal strokes (9.8%) and 8 nonfatal myocardial infarctions (9.8%) in the untreated group but no adverse events in the T treated group.

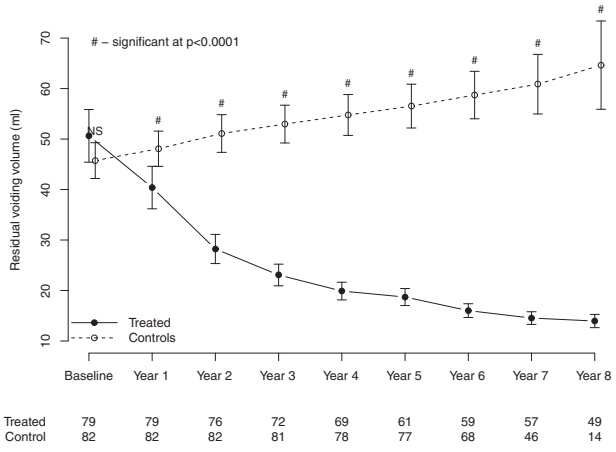

Figure 3. Post-void residual bladder volume in propensity matched, T treated and untreated groups during 8-year followup.

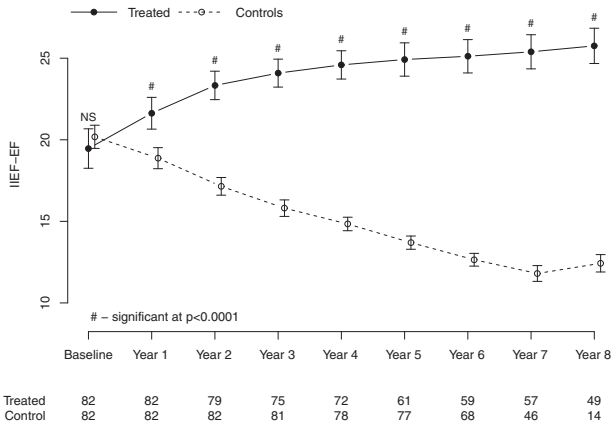

Figure 4. IIEF-EF in propensity matched T treated and untreated groups during 8-year followup.

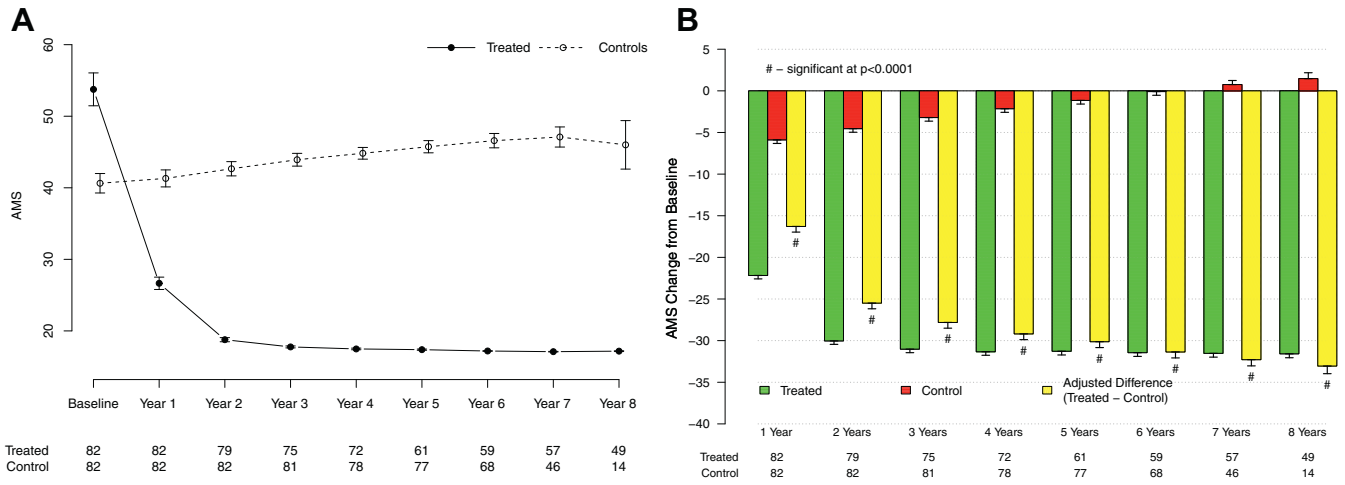

Figure 5. AMS. *A*, in propensity matched, T treated and untreated groups during 8-year followup. *B*, changes in T treated and untreated matched groups, and estimated differences between groups adjusted for baseline age, waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL, LDL, triglycerides and AMS.

DISCUSSION

Using propensity matching we compared data on 82 men receiving T therapy with data on 82 who remained untreated. Estimated mean differences between the groups were adjusted for baseline age, weight, waist circumference, fasting blood glucose, blood pressure, lipids and AMS.

We report that T therapy produced significant improvements in LUTS as assessed subjectively by I-PSS and objectively by the significant reduction in post-void bladder volume. Improvements in I-PSS and post-void bladder volume were progressive and sustained during the entire followup of approximately 8 years. Further analysis of I-PSS showed a clear difference between the treated and untreated groups.

Others also reported that T therapy significantly increased mean maximal bladder capacity and compliance ($p = 0.007$ and 0.032, respectively) while mean detrusor pressure at maximum urine flow significantly decreased from before to after treatment ($p = 0.017$).[14] As shown in an animal model these findings suggest that T improves LUTS/bladder function probably by increasing bladder capacity and compliance, and decreasing detrusor pressure at maximal flow.[15] In that animal model Tek et al found that orchiectomy decreased mean maximal bladder capacity by 38.91% ± 17.83% and T treatment increased maximal bladder capacity by 46.61% ± 20.82%. Hristov et al observed that T treatment decreased detrusor smooth muscle cell excitability by directly activating the large conductance voltage and Ca^2 activated K channels via nongenomic mechanisms.[16] Other studies have shown that T treatment induced bladder neck smooth muscle relaxation and rapid inhibition of contractility in detrusor smooth muscle preparations.[17,18] Such findings suggest that there are underlying T mediated physiological and anatomical mechanisms in bladder function.

Kim et al reported that marked differences exist in LUTS between obese and nonobese patients, including differences in voiding and storage symptoms.[19] The increased obesity associated with T deficiency and worsening LUTS may have a common pathophysiological mechanism. Obesity increases aromatase activity, leading to a state of T deficiency, while in the meantime the prostate continues to enlarge, worsening LUTS.[6] Since T therapy results in a sustained and marked decrease in body weight, waist circumference and BMI,[2] weight loss associated with T treatment may contribute to the observed improvement in LUTS. Our findings are also supported by a number of human and animal studies demonstrating a strong independent association between the components of metabolic syndrome and BPH/LUTS.[19] To our knowledge no conclusive data suggest that T therapy produces deleterious effects on I-PSS total scores, prostate volume or PSA,[9] or worsens LUTS.[5] Several other reports suggest that T therapy improves LUTS symptoms in men with T deficiency and mild BPH.[8,20,21]

We also report significant improvement in erectile function in response to T therapy. In this study we found that during the 8-year followup a marked increase in the IIEF-EF domain score was noted only in men on T therapy after adjustments for a host of variables. Our findings are consistent with reports on the role of T in sexual function.[3,22–24] In a previous study T therapy produced a significant decrease in the mean AMS score from 40.4 ± 7.3 to 28.8 ± 5.31 ($p = 0.001$) and it significantly increased the mean IIEF-5 score from 8.84 ± 3.76 to 14.36 ± 3.62 ($p = 0.001$).[14] We should point out that IIEF is

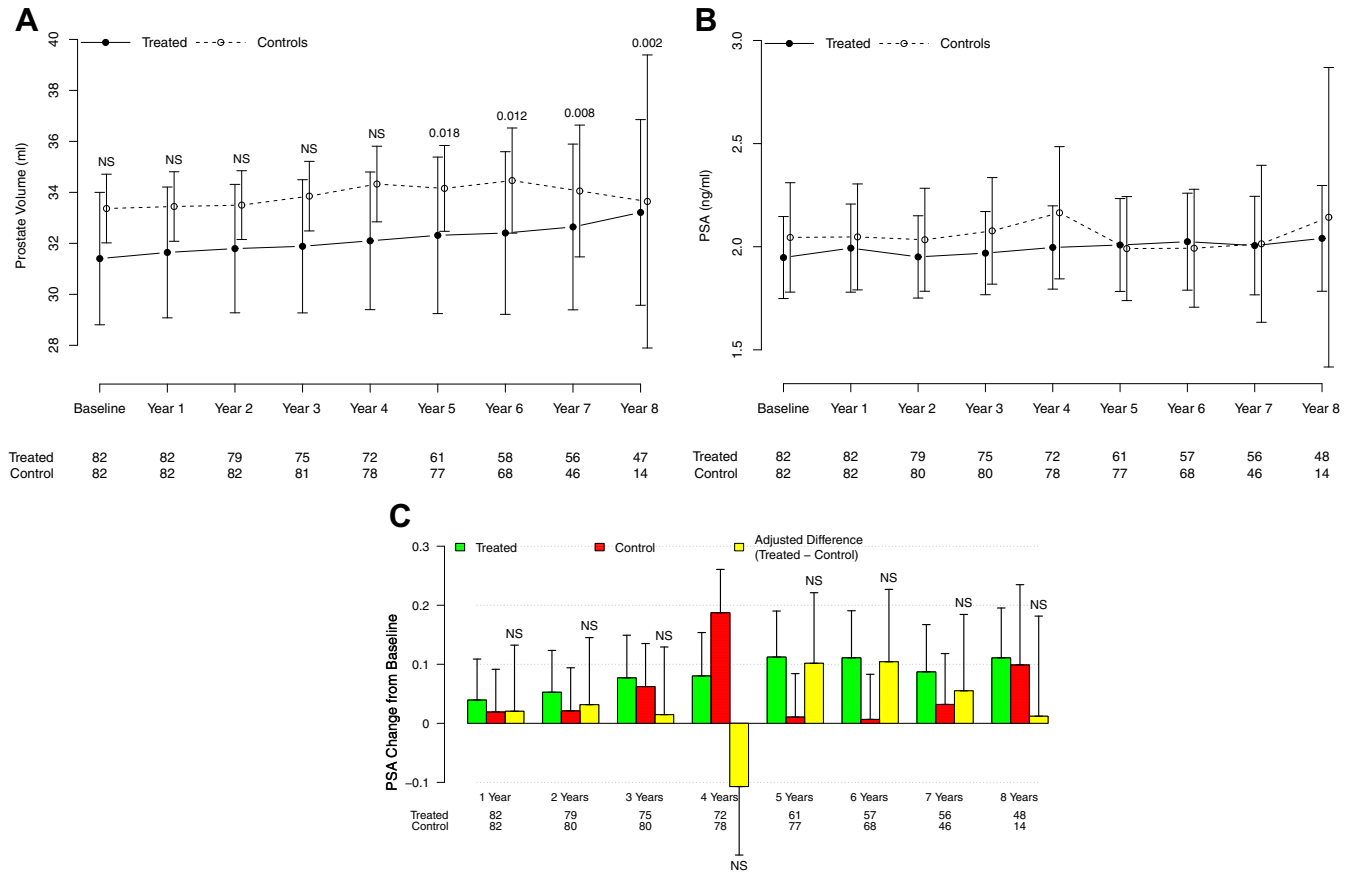

Figure 6. *A*, prostate volume in propensity matched, T treated and untreated groups during 8-year followup. *B*, PSA in propensity matched, T treated and untreated groups during 8-year followup. *C*, PSA changes in T treated and untreated matched groups, and estimated differences between groups adjusted for baseline age, waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL, LDL, triglycerides and AMS.

influenced by patient age, overall general health and voiding function. Since voiding function interrupts sleep due to awakening several times per night, it is likely to impact general health and reduce erectile function. Furthermore, weight gain and poor health also negatively impact erectile function.

Several studies have demonstrated that LUTS exert a negative impact on QoL and treatment of these symptoms significantly improves QoL and overall health.[19,20,25–28] In our series we further assessed health related QoL using the AMS scale. We observed a marked difference in AMS between the T treated vs the untreated group, suggesting that the untreated group may encounter worse somatic, psychological and sexual experiences. T therapy improves depression, bone mineral density, energy, libido, erectile function, muscle mass, insulin resistance and LUTS.[29] In men with type 2 diabetes reduced circulating T levels and ED severity have independently correlated with poor physical and social function, vitality and a decrease in the general health domains of the SF-36® health related QoL questionnaire.[30] Furthermore, ED and low T are markers of poor health that impact individual self-perception of health status.

One limitation of this study is that patients were not randomized. However, the decision for or against T therapy was not possible in all patients. Those with Klinefelter syndrome and other forms of primary hypogonadism had no choice and invariably received T therapy, as did patients with inflammatory bowel disease who were specifically referred to be treated with testosterone. The fact that these 3 subgroups were considerably younger explains the age gap between the T group and the control group. We should also point out that potential selection bias may have existed based on socioeconomic status, which is a factor well known to influence overall and cardiovascular health. Another limitation is that we did not have any information on medication adherence in regard to any concomitant medications that the patients had been prescribed.

CONCLUSIONS

Long-term T therapy in men with T deficiency was well tolerated with excellent adherence, suggesting a high level of patient satisfaction. Progressive sustained improvement in urinary and sexual function was recorded in men who received long-term T therapy, contributing to overall improvement in QoL. In untreated hypogonadal controls voiding and erectile function deteriorated with continued followup. These findings suggest that T therapy improves urinary and sexual function as well as QoL.

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EDITORIAL COMMENT

Haider et al detail the results of an observational registry study of outcomes in men with symptomatic hypogonadism, comparing 7-year outcomes in those on testosterone therapy vs those not treated. They report several interesting findings, including significant improvement in voiding function, erectile function and quality of life, in men on testosterone therapy vs those not treated.

They also report that there were 5 deaths (6.1%), 8 nonfatal strokes (9.8%) and 8 nonfatal myocardial infarctions (9.8%) in the untreated group but no adverse cardiovascular events in the group treated with testosterone. The striking difference in cardiovascular outcomes in this study might be interpreted by some as meaning that testosterone therapy provides a protective effect against cardiovascular events. To their credit the authors do not assert this claim as the study was not specifically designed to assess the effects of testosterone on cardiovascular outcomes. The disparity between the 2 groups might simply underscore the inherent limitations of a registry study, including the lack of placebo control and randomization.[1]

The issue of hypogonadism, testosterone therapy and cardiovascular outcomes has garnered much controversy in the last several years.[2,3] Readers should understand that this study does not provide the clarifying data to resolve that debate.

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REPLY BY AUTHORS

We fully agree with the comment that disparities between the treated and untreated groups in our registry might underscore some inherent limitations, ie the absence of a placebo control and randomization. However, we attempted to use propensity matching to adjust for a number of factors, which would have reduced potential confounding.

We agree that no single study can provide complete evidence to resolve the ongoing debate regarding the controversy of testosterone therapy and cardiovascular disease irrespective of whether it is a randomized clinical trial, a meta-analysis or an observational study. Nevertheless, we wish to point out a large observational study published recently with a population of 8,808 men (19.8%) who were ever dispensed testosterone therapy and 35,527 (80.2%) who were never dispensed T therapy.[1] Of this population of 44,335 men 43,049 (97.1%) were entered in the cohort based on serum T less than 300 ng/dl and 1,286 (2.9%) were entered based on a diagnosis of T deficiency. The study concluded that "Among men with androgen deficiency, dispensed testosterone prescriptions were associated with a lower risk of CV [cardiovascular] outcomes during a median 3.4 years of followup."[1]

We should also point out that while a dim view of T therapy has been propagated regarding evidence derived from observational studies, one must also appreciate the limitations of randomized clinical trials. As revealed in a number of studies[2,3] real life clinical data can be synthesized from observational studies which are critical to meet health care challenges in the era of shrinking resources. In sum the evidence derived from available studies irrespective of the study nature should be applied by physicians, patients and policy makers to make decisions regarding patient care.

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