Testosterone Gel Monotherapy Improves Sexual Function of Hypogonadal Men Mainly Through Restoring Erection: Evaluation by IIEF Score

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OBJECTIVES To use the International Index of Erectile Function (IIEF) to evaluate the improvement of erectile function and other sexual functions after testosterone monotherapy. Testosterone replacement therapy alone was reported to be effective for the improvement in sexual function in hypogonadal males. However, it is still unclear that which kind of the sexual function is most beneficial and to what extent the sexual function could be improved.

METHODS A double-blind, randomized, placebo-controlled study was conducted with a treatment group (n = 20) and control group (n = 20). Using a critical review of the different sexual functional domain scores of the IIEF-15 and the scores of the IIEF-5, we evaluated the sexual function of men in hypogonadal status before and after 3 months of testosterone gel treatment. Effect size was used to compare the drug effects for each sexual functional domain, and the results were confirmed by multivariate analysis.

RESULTS A total of 30 men remained at the end of the study. After 3 months of testosterone gel therapy for the hypogonadal men, the most beneficial effect on sexual function was erectile function, with sexual desire and orgasmic satisfaction insignificantly affected.

CONCLUSIONS The results of our study have shown that transdermal testosterone gel treatment for hypogonadal patients can improve their sexual dysfunction mainly through restoring erectile function. UROLOGY 73: 762–766, 2009. © 2009 Elsevier Inc.

Testosterone is the main sexual hormone in human males, with a profound effect on the physiology of sexual function. A meta-analysis indicated a 57% clinical response rate to testosterone therapy in patients with erectile dysfunction (ED), a 64% response rate in those with primary hypogonadism, and a 44% response rate in those with secondary hypogonadism.[1] Testosterone replacement therapy for hypogonadal men has proved to be effective at improving different kinds of sexual function, including the sexual desire, erection, sexual performance, and sexual attitudes[2-4] of patients with hypogonadal ED. In a clinical trial of testosterone monotherapy with transdermal gel formulation, maximal improvement in sexual function had occurred by day 30 and continued for the entire 6 months of the study.[5] The beneficial effects on sexual function were reported to be maintained with long-term treatment with testosterone gel.[6] However, Shabsigh et al.[7] reported a response to testosterone treatment with improvement of the International Index of Erection Function (IIEF) score at week 4 but a nonsignificant response on the IIEF at the end of the study (week 12). All sexual function evaluations in previous trials for testosterone monotherapy were performed using patient sexual diaries or questionnaires. Also, the results only reflected the overall sexual function. In contrast, recent studies on the effect of phosphodiasterase-5 (PDE-5) inhibitors focused solely on erection, even though the measurements used the IIEF. Attention should also be paid to the different sexual function domain scores, and comparative studies for drug effects on different domains of sexual functions should be conducted.

In the present study, we specifically evaluated the effects of a transdermal testosterone gel (TTG) on the extent of improvement for different kinds of sexual function in hypogonadal male patients. Using a critical review of the IIEF-15 and IIEF-5 scores before and after treatment, we attempted to determine which sexual function domain obtained the most benefits and to what extent sexual function could be improved with testoster-

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Submitted: May 16, 2008, accepted (with revisions): October 21, 2008

0090-4295/09/$34.00
doi:10.1016/j.urology.2008.10.019

one monotherapy. This tool was proposed to provide information concerning how testosterone replacement therapy can improve the sexual function of hypogonadal men.

MATERIAL AND METHODS

Patients

A total of 77 hypogonadal Taiwanese men with (a) a morning serum total testosterone concentration of <300 ng/dL, or (b) a total testosterone level that had been once marginally ≥300 ng/dL, with the value of the morning serum free testosterone level <8.7 pg/mL, were recruited from the urology clinic for the present study. Their age was 20-75 years. All the patients signed an informed consent form that had been approved by the institutional review board. They were screened using medical and sexual history, physical examination, and endocrine evaluation. Eligible subjects were men who had not taken hormonal replacement therapy for ≥6 weeks before the study began. They were required to have had a stable, monogamous heterosexual relationship of ≥6 months' duration. None of the patients had ever used PDE inhibitors or any kind of treatment for their sexual dysfunction.

Study Design and Medications

This was a double-blind, randomized, placebo-controlled, 3-month study of TTG monotherapy (AndroGel, Solvay Pharmaceuticals, Marietta, GA). The treatment group received 50 mg testosterone gel in 5-g sachets, and the placebo group received a placebo gel. No distinguishable feature could be noted between the TTG and the placebo. All the patients were instructed to apply the gel once daily to 2 alternating application sites, such as the shoulder, upper arm, and/or abdomen.

At the initial screening visit, all subjects who fulfilled the selection criteria completed the complete IIEF and International Prostate Symptom Score questionnaires. The total testosterone and free testosterone levels were checked twice, 1 week apart, before the men were enrolled for the baseline assessment (visit 2), and the data of the latter value was set as the baseline. Laboratory examination of prostate-specific antigen and other hormone test profiles was performed using a radioimmunoassay kit. At each of the 3 treatment visits, approximately 30 ± 3 days apart, the following tests were done: total testosterone, free testosterone, physical examination, and safety evaluation, including adverse events and skin irritation assessment of the concomitant medications. On the final visit, all the safety evaluation and hormonal data were completed for each subject. The sexual function evaluation with the IIEF questionnaires[8] was performed in detail, including the 15-item scores and 5 functional domain scores. Erectile function (EF), orgasmic function (OF), sexual desire (SD), satisfaction with intercourse (IS), and overall satisfaction (OS) were assessed by summing the scores assigned to the related individual questions in each domain.

Statistical Analysis

Two-way analysis of variance, with fixed-factor treatment by subject, was used to compare the primary and secondary efficacy endpoints and safety parameters between the 2 treatment groups. If the treatment-by-subject interaction was not statistically significant ($P \geq .10$), the interaction term was dropped from the analysis of variance model. The paired t test was used to test the changes from the baseline within each treatment group.

Comparisons of the drug effects for each functional domain of sexual function were evaluated by the "effect size." Eta squared (η^2) is one of the "effect size" indexes.[9] It is used as a strength-of-effect measure when a statistically significant value of F occurs. Eta squared is calculated by multiplying the degrees of freedom (dfA) by the F value and then dividing the product by a dfA × F plus error term (df_{error}). It is a measure to reduce the error predicted in and among groups and then to determine the level of an independent variable. The equation is as follows:

$$\eta^2 = \frac{SS_A}{SS_{Total}} = \frac{(df_A)(F_{obs})}{(df_A)(F_{obs}) + df_{error}}$$

RESULTS

A total of 40 eligible men were randomized to receive TTG 50 mg/d (treatment group) or placebo. Three patients in the placebo group were withdrawn from the study because of adverse events. Two of them were drug-related adverse events (skin rash and dermatitis). The other was a nondrug-related event (abdominal pain). Seven patients did not complete the follow-up of either the biochemical tests or questionnaires and were thus excluded from the analysis. Thus, 30 patients (15 in the treatment group and 15 in the control group) who completed the whole evaluation, including the IIEF-15 and IIEF-5 questionnaires in the 3-month study. The power of the study was calculated, and the power was >90% at the beginning of the study. No statistically significant differences were found in the baseline data of the testosterone level between the TTG group and the placebo group.

After 3 months of TTG therapy, the increase in the serum testosterone level was prominent in the AndroGel group. The pretreatment hypogonadal status was converted to normal, and the difference was statistically significant in the first and second months (Table 1). Compared with the treatment result in the placebo group, the effect of the increase in the serum free testosterone level was also statistically significant in the second month. Together with the results of the serum prostate-specific antigen measurement and International Prostate Symptom Score, no definite change was noted in the findings of the follow-up digital rectal examination of the prostate. These results indicate that no adverse effects occurred in the prostate with 3 months of testosterone replacement therapy. The improvement in sexual function was obvious through the assessment of the IIEF score comparisons (Table 1).

Although the total score of IIEF-15 significantly increased in the TTG group after 3 months of treatment application, not all of the sexual function domains had the same result. In the TTG group, the IIEF scores of the sexual desire (SD) and overall satisfaction (OS) function domains did not significantly increase compared with those of the placebo group. Only the improvements in EF, OF, and IS were statistically significant ($P < .01$)

Table 1. Change from baseline of serum total testosterone, free testosterone, PSA, IPSS, and IIEF-15 after transdermal testosterone gel treatment

	AndroGel Group			Placebo Group			Between Group Difference (*P* Value)
	1 mo	2 mo	3 mo	1 mo	2 mo	3 mo	
TT (ng/dL)	179.6 ± 328.7*	171.1 ± 313.9*	117.6 ± 342.1	18.2 ± 68.6	12.2 ± 105.2	3.4 ± 90.6	
FT (ng/dL)	4.72 ± 8.31*	7.79 ± 10.71*	6.58 ± 14.64	1.75 ± 7.58	0.31 ± 5.25	−0.04 ± 4.41	.014 in 2nd mo
PSA (ng/dL)			0.074 ± 0.208			−0.069 ± 0.436	.213
IPSS			−1.6 ± 3.8			−2.1 ± 5.4	.769
IIEF-15 score			14.4 ± 15.9			−5.2 ± 15.3	.002

PSA, prostate-specific antigen; IPSS, International Prostate Symptom Score; IIEF, International Index of Erectile Function; TT, total testosterone; FT, free testosterone.

Baseline data of TT, FT, PSA, IPSS, and IIEF-15 score in AndroGel group was 183.5 ± 246.7, 5.1 ± 3.9, 1.0 ± 0.8, 6.2 ± 4.6, and 10.7 ± 4.9, respectively; corresponding baseline data for placebo group were 177.5 ± 147.8, 4.9 ± 3.8, 0.7 ± 1.1, 5.9 ± 3.5, and 13.9 ± 6.6.

* Change from baseline statistically significant within group.

compared with the results in the placebo group. When we calculated the effect size of the 5 different sexual function domains after AndroGel treatment, EF exhibited the most prominent effect, IS and OF were also effectively increased, and SD and OS were affected insignificantly (Table 2). The result was double checked using another statistical tool of multivariate analysis. That result also showed that the testosterone effect for each functional domain was significantly different between the AndroGel and placebo groups ($P = .075$). The IIEF-5 has been proved to be a reliable test for the diagnosis of the presence and severity of ED.[10] The IIEF-5 was reorganized using IIEF question 15 (erection confidence), question 2 (erection firmness), question 4 (erection frequency), question 5 (ability to maintain an erection), and question 7 (intercourse satisfaction). The IIEF-5 has been validated and tested in Taiwan.[11] A patient's total score of IIEF-5 of ≤15 suggests that the patient has ED. In the present study, patients of both groups had ED at baseline (AndroGel group score 10.7 ± 4.9 and placebo group score 13.9 ± 6.6). After 2 months of treatment, the patients' total score on the IIEF-5 in the AndroGel group had increased to 16.9 ± 5.1, beyond the cutoff level for ED in Taiwan. In contrast, the patients' total score on the IIEF-5 in the placebo group had decreased to 12.2 ± 7.0, remaining within the range indicating ED. The change in EF after AndroGel treatment was significant (Table 3).

COMMENT

Androgens are thought to be essential for maintaining male sexual function according to experimental and clinical evidence with various mechanisms. Studies of castrated rats have provided physiologic and morphologic evidence of an androgen-dependent effect on penile erection.[12,13] Clinical observations of men after surgical or medical castration have also suggested that androgens have a prominent effect on the male sexual libido and EF.[14-16] It was reported that 12% of men with ED also had subnormal testosterone levels.[17] Various complaints of sexual dysfunction are known to be important diagnostic criteria of androgen deficiency in the aging man.[18,19] Testosterone replacement therapy has been shown to effectively increase the serum testosterone level and to improve sexual desire, activity, and frequency in patients with male hypogonadism.[20,21] The testosterone threshold for sexual desire in men is very low, and most of the improvement in sexual function after testosterone therapy might not be mediated by the libido.[22-24] More and more studies have shown that androgens exert a direct effect on penile tissue for maintaining EF. Androgen deficiency might produce metabolic and structural imbalances in the corpus cavernous that directly cause ED.[25,26] Testosterone monotherapy has been observed to improve EF and vascular parameters in 36% and 42% of patients, respectively.[27]

Table 2. Change from baseline of total and different sexual functions assessed by IIEF-15 scores and 5 sexual function domains after 3 months of testosterone therapy

	AndroGel Group		Placebo Group		Difference	Effect
IIEF 15	Baseline	Difference	Baseline	Difference	(*P* Value)	Size*
Total score	34.1 ± 14.0	14.4 ± 15.9 (*P* = .003)	42.4 ± 16.8	−5.2 ± 15.3 (*P* = .209)	.002	
EF	13.3 ± 6.8	7.3 ± 7.8 (*P* = .003)	16.9 ± 8.2	−1.6 ± 8.5 (*P* = .476)	.007	0.173
OF	6.0 ± 3.1	2.1 ± 3.5 (*P* = .036)	6.3 ± 3.2	−2.0 ± 3.5 (*P* = .045)	.004	0.042
SD	5.0 ± 1.6	1.4 ± 1.8 (*P* = .008)	6.3 ± 2.4	0.0 ± 2.3 (*P* = 1.0)	.086	0.005
IS	5.5 ± 3.2	2.3 ± 3.1 (*P* = .011)	6.7 ± 3.8	−1.9 ± 4.0 (*P* = .089)	.004	0.045
OS	4.4 ± 1.1	1.3 ± 1.9 (*P* = .017)	6.2 ± 2.3	0.3 ± 2.8 (*P* = .719)	.246	0.003

IIEF, International Index of Erectile Function; EF, erectile function; OF, orgasmic function; SD, sexual desire; IS, intercourse satisfaction; OS, overall satisfaction.

EF sum of IIEF questions 1-5 and 15 (score range 1-30); OF sum of IIEF questions 9 and 10 (score range 0-10); SD sum of IIEF questions 11 and 12 (score range 2-10); IS sum of IIEF questions 6-8 (score range 0-15); OS sum of IIEF questions 13 and 14 (score range 2-10).

* See text for definition and equation for effect size.

Table 3. Erectile function of patients before and after testosterone therapy in both groups evaluated by IIEF-5

	AndroGel Group			Placebo Group			
IIEF-5	Baseline	After Treatment	Change	Baseline	After Treatment	Change	Group Difference
Q15, confidence	2.0 ± 0.7	2.8 ± 0.9	0.8 ± 0.9 (*P* = .005)	2.9 ± 1.2	3.0 ± 1.4	0.1 ± 1.6	0.189
Q2, firmness	1.8 ± 1.2	3.4 ± 1.5	1.6 ± 1.4 (*P* < .001)	2.6 ± 1.6	2.0 ± 2.1	−0.6 ± 1.8	0.001
Q4, maintain frequency	2.2 ± 1.4	3.8 ± 1.1	1.6 ± 1.7 (*P* = .003)	2.7 ± 1.6	2.5 ± 2.0	−0.3 ± 1.9	0.011
Q5, maintain ability	2.7 ± 1.4	3.9 ± 1.2	1.2 ± 0.8 (*P* = .021)	3.0 ± 1.6	3.0 ± 2.0	0.0 ± 2.4	0.153
Q7, IS	2.1 ± 1.2	3.1 ± 1.3	1.0 ± 1.5 (*P* = .019)	2.7 ± 1.7	1.7 ± 1.8	−1.0 ± 1.6	0.002
Total score	10.7 ± 4.9	16.9 ± 5.1*	6.2 ± 5.9 (*P* = .001)	13.9 ± 6.6	12.2 ± 7.0	−1.7 ± 6.9	0.003

IIEF, International Index of Erectile Function; Q, question.

* Total IIEF-5 score of AndroGel group was >15, greater than Taiwanese cutoff for ED.

Through the use of clinical assessment of the IIEF-15 questionnaire scores in the present study, the general sexual function of hypogonadal men improved significantly as the serum total testosterone and free testosterone concentrations increased to normal levels after TTG treatment. Compared with the placebo group, the increases in the IIEF-15, total score, EF domain score, OF domain score, and IS domain score from the baseline values were significant. When the effect on different sexual function domains was analyzed, we found that testosterone might be most beneficial to EF, followed by OF and IS, and then SD and OS (Table 2). The improvement in ED might be the fundamental parameter for restoring patients' sexual function and affect other sexual functions such as OF and IS. Nevertheless, after 3 months of testosterone monotherapy, the change in the OS domain score and SD function domain score from baseline in the TTG group itself was still significant (P = .017 and P = .008, respectively; Table 2). Human sexuality is truly a complex phenomenon, and many factors are related to sexual desire, sexual orgasm, and overall sexual satisfaction. Testosterone therapy alone, and even in combination with PDE5 inhibitors, might not improve sexual desire, sexual orgasm, or overall sexual satisfaction because of other existing problems such as a poor relationship with a partner.

We used the IIEF-5 Chinese version questionnaire to evaluate the prevalence of ED in Taiwanese men >40 years old and then compared the results with those of other prevalence studies of ED in Taiwan and found that the result using IIEF-5 was even more accurate in the diagnosis of ED.[28] In the present study, the average total IIEF-5 score for the patients in the TTG group had increased to 16.9 ± 5.1 after 3 months of treatment (Table 3). Although testosterone monotherapy might enhance the EF of hypogonadal men only to a certain degree, the erection's hardness might be enough for penetration, with a totally different result in sexual performance and satisfaction. On the basis of our previous study of patients after successful penile prosthesis implantation, satisfaction with an erection and intercourse and the occurrence of sexual orgasm can directly affect the quality of life, self-esteem, and self-confidence of men with long-term ED.[29] An improvement in erections might be the most prominent therapeutic effect of hypogonadal men and could further increase patients' mood, sexual desire, and overall sexual satisfaction and correct other androgen-deficient symptoms.

The IIEF-15 and IIEF-5 questionnaires were developed as instruments to assess EF. The results of the present study have provided the information that testosterone monotherapy is very beneficial to the EF of hypogonadal men when evaluated using the IIEF questionnaire. However, compared with the results of the clinical trials of the PDE-5 inhibitors, the improvement in erections with testosterone monotherapy is not yet optimal. Nevertheless, with an increasing dosage of testosterone, ED can be improved further with this combination.[30]

This study had limitations. The sample size was small, and ≤25% of the patients were withdrawn or excluded from the analysis because of side effects or incomplete data. Also, the population of this study was only Taiwanese men. In addition, the variation in age was rather large. Finally, although the power of the study was sufficient at the beginning, with the decreased sample size, the power might not have been enough. However, the results of the present study have provided a method to evaluate the effect of medication on different domains of sexual function. With this information, we will be capable of helping patients who are taking medication for their sexual function without fully satisfactory results.

CONCLUSIONS

TTG monotherapy for hypogonadal male patients can improve their sexual dysfunction. Through the IIEF questionnaire score evaluation, we found the improvement was mainly through restoring patients' EF and that the SD functional domain and OS were not significantly affected by testosterone monotherapy. The IIEF-5 score analysis showed that at the endpoint of testosterone treatment, most patients had improved EF. However, they still had a status of mild ED. Combination therapy with an androgen and PDE-5 inhibitors might enhance EF and thus further improve the other sexual functions such as SD and OS.

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