Does Sildenafil Combined with Testosterone Gel Improve Erectile Dysfunction in Hypogonadal Men in Whom Testosterone Supplement Therapy Alone Failed?

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ABSTRACT

Purpose: We evaluated the efficacy of testosterone gel (T-gel) alone and in combination with sildenafil in hypogonadal patients with erectile dysfunction (ED).

Materials and Methods: A total of 49 hypogonadal men (mean age 60.7 years) with ED participated for a mean of 20.2 months. Blood was tested for total and bioavailable testosterone, and prostate specific antigen. Sexual function was assessed using the International Index of Erectile Function questionnaire and a global assessment question (GAQ). Men received 1% 5 gm T-gel for 6 months, and 100 mg sildenafil was added to those with a “no” response to the GAQ after 3 months on testosterone supplement.

Results: A total of 31 patients reported significant improvement in the sexual desire domain (from a mean ± SD of 4.2 ± 0.8 to 8.6 ± 0.4) and erectile function (EF) domain (from 13.6 ± 1.9 to 27 ± 0.8) following treatment with testosterone supplement alone. One patient was excluded from study after urinary retention developed and 9 reported irritation at the gel application site. In spite of normalization of total and bioavailable testosterone values, and significant improvement of sexual desire domain scores, the EF of 17 men remained less than 26 or they responded “no” to the GAQ. These men received combined T-gel and sildenafil, after which all graded EF greater than 26 and responded positively to the GAQ.

Conclusions: Combined treatment with sildenafil and T-gel has a beneficial effect on ED in hypogonadal patients in whom treatment with testosterone supplement alone failed.

KEY WORDS: impotence, phosphodiesterase inhibitors, testosterone

Androgens have a profound role in male sexual function and in erectile physiology.1 Monga et al reported that hypogonadal patients with erectile dysfunction (ED) may benefit from testosterone supplement by achieving improved quality of erections and libido,2 and Mulhall et al questioned the role from testosterone supplement by achieving improved quality nadal patients with erectile dysfunction (ED) may benefit

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alone, patients not satisfied with EF (a “no” answer to the GAQ) were treated with a combination of sildenafil and TS for another 3 months. These patients comprised the combination therapy group. All study parameters were reevaluated after another 3 months. Data were analyzed using 1- and 2-way analysis of variation with repeated measures.

RESULTS

A total of 49 men (age range 35 to 74 years) comprised the study cohort. Each had at least 1 comorbidity such as hypertension, diabetes mellitus, or cardiovascular disease, not taking nitrates, that could potentially contribute to the ED. Mean ED duration was 20.2 months (range 2 to 48 months). None of our patients had a body mass index greater than 30 kg/m². All patients achieved normal TT and BT levels, and an improvement in sexual desire (SD) domain score (from 4 ± 0.8 to 8.4 ± 1.8, p <0.001) 3 months after TS initiation (table 1). Following treatment with T-gel 31 of the 49 participants (63.3%) reported significant improvement in the SD domain (from a mean of 4.0 to 8.9 ± 0.5, p <0.001) and in the EF domain (from a mean of 15.0 ± 1.9 to 26 ± 2.2, p <0.001, part A of figure). All patients in this group were satisfied with TS alone and answered “yes” to the GAQ, thus comprising the TS alone group.

A total of 17 patients answered “no” to the GAQ in spite of normalization of TT and BT values, significant improvement of SD domain scores and improvement of the EF domain from a mean of 13.6 ± 1.9 to 22 ± 1.9 following T-gel alone. The EF domain score of each of these patients remained less than 26. Those 17 patients were treated with a combination of T-gel and sildenafil for another 3 months, and comprised the combination therapy group. After 3 months of combination therapy there was no statistically significant improvement in mean EF score (to 27 ± 1.9 following T-gel alone). The effects of testosterone during embryonic differentiation and pubertal development are well delineated, but the causal relationship between altered androgen levels and ED has not yet been established. Greenstein et al reported that men may still have functional erections with castration blood levels of testosterone but the National Institutes of Health Consensus Development Panel on Impotence concluded that some hypogonadal men with ED may benefit from testosterone supplementation. Evaluation of blood level of testosterone is a fundamental step in the search for a correctable/reversible cause of ED. Abnormal testosterone levels in men with ED were reported to be 5.7% to 18.7% by Bodie et al and Earle and Stuckey. Thus, management of hyponadism with TS may restore sexual function and achieve significant benefits in terms of libido, general well-being, osteoporosis, muscle

### Table 1. Blood testosterone components over time in all study patients

<table>
<thead>
<tr>
<th>Component</th>
<th>Mean ± SD Baseline</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>p Value (before vs after treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT (ng/ml)</td>
<td>3.78 ± 0.21</td>
<td>10.13 ± 1.60</td>
<td>10.2 ± 1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BT (ng/ml)</td>
<td>0.60 ± 0.09</td>
<td>1.09 ± 0.09</td>
<td>1.1 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% BT</td>
<td>17.35 ± 1.31</td>
<td>26.43 ± 2.31</td>
<td>25.96 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>2.9 ± 0.7</td>
<td>2.1 ± 0.7</td>
<td>1.88 ± 0.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>I-PSS</td>
<td>9.9 ± 2.7</td>
<td>10.1 ± 4</td>
<td>9.8 ± 3.2</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

DISCUSSION

The effects of testosterone during embryonic differentiation and pubertal development are well delineated, but the causal relationship between altered androgen levels and ED has not yet been established. Greenstein et al reported that men may still have functional erections with castration blood levels of testosterone but the National Institutes of Health Consensus Development Panel on Impotence concluded that some hypogonadal men with ED may benefit from testosterone supplementation. Evaluation of blood level of testosterone is a fundamental step in the search for a correctable/reversible cause of ED. Abnormal testosterone levels in men with ED were reported to be 5.7% to 18.7% by Bodie et al and Earle and Stuckey. Thus, management of hyponadism with TS may restore sexual function and achieve significant benefits in terms of libido, general well-being, osteoporosis, muscle

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**Table 2. Study group baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>T-Gel</th>
<th>T-Gel + Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Mean pt age (range)</td>
<td>61.8 (36-73)</td>
<td>58.9 (35-74)</td>
</tr>
<tr>
<td>Mean mos ED (range)</td>
<td>17 (6-20)</td>
<td>21 (6-26)</td>
</tr>
<tr>
<td>Mean pretreatment ng/ml testosterone ± SD</td>
<td>3.74 ± 0.19</td>
<td>3.85 ± 0.14</td>
</tr>
<tr>
<td>Mean ng/ml BT ± SD</td>
<td>0.61 ± 0.1</td>
<td>0.59 ± 0.08</td>
</tr>
<tr>
<td>Mean % BT ± SD</td>
<td>17.82 ± 0.9</td>
<td>16.5 ± 1.96</td>
</tr>
<tr>
<td>Mean ng/ml PSA ± SD</td>
<td>2.2 ± 0.7</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>Mean I-PSS ± SD</td>
<td>10.3 ± 1.8</td>
<td>9.18 ± 3.2</td>
</tr>
</tbody>
</table>

p Value not significant.
strength, mental acuity and growth hormone levels, all of which may be negatively affected by low testosterone levels.1

Traditional TS therapy has been found ineffective in restoring EF in a considerable number of hypogonadal men. Morales et al reported that the oral testosterone undecanoate restored plasma testosterone levels in all patients, and that 61% had an improvement in sexual attitudes and performance.12 The testosterone esters enanthate and cypionate require injection of the medication every 10 to 21 days. This TS is rapid and effective therapy but it bears a significant disadvantage due to a roller-coaster effect, leading to fluctuation in mood, libido and energy levels, and perhaps causing breast tenderness and gynecomastia.1,13 Transdermal testosterone therapy is the most effective route for restoring the circadian pattern of testosterone production of the testes.1 T-gel supplement was found to be effective in restoring testosterone blood levels, improving sexual function and mood, increasing lean mass and muscle strength, and decreasing fat mass in hypogonadal men with less skin irritation and fewer cases of discontinuation compared to the recommended dose of a testosterone patch.13 In our study after 3 months of T-gel application normalization of testosterone blood level was achieved in all patients with 63.3% reporting significant improvement in the SD and EF domains. Our results are similar to those with oral, transdermal patch and intramuscular TS.12,13

Hypogonadism is rarely the main or the single explanation for ED.14 Thus, it is reasonable that not all hypogonadal men in the current study had improved EF after normalization of blood testosterone alone. This group of patients did benefit from the combination treatment of sildenafil and T-gel, thus the hypogonadal effect on ED was, indeed, the main one among men who were satisfied with T-gel alone, insofar as the hypogonadal effect on ED was, indeed, the main one among men who were satisfied with T-gel alone, insofar as sexual function improved without further intervention. Co morbidity components probably had a greater etiological role in the combination treatment group. Morelli et al demonstrated that androgens positively regulate phosphodiesterase type 5 in rabbit corpora cavernosa strips.15 Their data may explain the effect of combined sildenafil and T-gel in improving IIEF scores in all patients in the combination therapy group. Aversa et al reported that short-term transdermal testosterone supplement (5 mg daily) in patients with ED showing testosterone levels in the low to normal range and not responding to sildenafil alone because of arterial insufficiency (evaluated by dynamic color duplex ultrasound) led to higher arterial inflow to the penis and better cavernous vasodilatation improvement in the erectile response to sildenafil.16 At first glance it would seem easier to give sildenafil to hypogonadal men as first line therapy for ED, but sildenafil alone appears to be less effective in men with hypogonadism. Kalinchenko et al evaluated the effect of oral testosterone undecanoate on ED associated with diabetes mellitus in patients in whom sildenafil therapy alone failed.17 Oral testosterone treatment alone restored testosterone blood levels to normal and increased libido, while combined sildenafil therapy with oral testosterone supplement induced satisfactory erections as assessed by the IIEF scale in 84 of 120 (70%) sildenafil nonresponders.17 Shabsigh et al compared the efficacy of T-gel versus placebo as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who did not respond to sildenafil alone, and concluded that T-gel taken with sildenafil may be beneficial in improving erectile function.4 It seems that for a favorable improvement of EF in hypogonadal men there may be a need for combined therapy with testosterone supplement and sildenafil.

Two patients discontinued treatment due to urination difficulties. A possible explanation for one case is the effect of TS on prostate size affecting bladder outlet obstruction. As in all patients in their 50s and older, monitoring for prostate cancer using PSA measurements and digital rectal examination is recommended for hypogonadal men who are undergoing TS therapy.

CONCLUSIONS

Our results suggest that T-gel is an effective and safe treatment for hypogonadal patients with impaired sexual function. The combination of sildenafil and T-gel has a beneficial effect on hypogonadal patients with erectile dysfunction whose condition did not improve satisfactorily with T-gel treatment alone.

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REFERENCES