

## ORIGINAL ARTICLE

# Efficacy of changing testosterone gel preparations (AndroGel or Testim) among suboptimally responsive hypogonadal men

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The study objective was to evaluate the efficacy of changing testosterone gel preparations among suboptimally responsive hypogonadal men. The records of all hypogonadal men on gel (Testim or AndroGel) testosterone replacement therapy (TRT) were reviewed to identify men who underwent a brand substitution in gel TRT due to initial suboptimal response. Total and free serum testosterone levels and the presence of hypogonadal symptoms (ADAM) were compared pre- and post-gel substitution. Of the 370 hypogonadal men on testosterone gel replacement therapy, 75 (20%) underwent a brand substitution. Prior to substitution, among patients initially treated with AndroGel, the mean total and free testosterone levels were  $311 \text{ ng dl}^{-1}$  and  $10.4 \text{ pg ml}^{-1}$ , respectively. Total testosterone levels were below  $300 \text{ ng dl}^{-1}$  in 58% of these patients. Following a change to Testim, mean total and free testosterone levels increased to  $484 \text{ ng dl}^{-1}$  ( $P < 0.001$ ) and  $14.6 \text{ pg ml}^{-1}$  ( $P = 0.01$ ), respectively. Total testosterone levels remained below  $300 \text{ ng dl}^{-1}$  in only 17% of these patients. Among patients initially treated with Testim, the mean total and free testosterone levels were  $544 \text{ ng dl}^{-1}$  and  $18.0 \text{ pg ml}^{-1}$ , respectively. Total testosterone levels were below  $300 \text{ ng dl}^{-1}$  in 15% of men. Following testosterone gel change to AndroGel, mean total and free testosterone levels were  $522 \text{ ng dl}^{-1}$  ( $P = 0.7$ ) and  $16.1 \text{ pg ml}^{-1}$  ( $P = 0.6$ ), respectively. Total testosterone levels remained below  $300 \text{ ng dl}^{-1}$  in 27% of these patients. Hypogonadal symptoms improved in a significant proportion of men who underwent a brand substitution following an initial suboptimal biochemical or symptomatic response. A change in testosterone gel preparation among initially unresponsive hypogonadal men is justified prior to abandoning or considering more invasive TRT. Changing from AndroGel to Testim offers hypogonadal men the potential for improved clinical and biochemical responsiveness. Changing from Testim to AndroGel is indicated to eliminate or minimize unwanted side effects.

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## Introduction

Hypogonadism is common and increases with age in men as serum testosterone levels gradually decline. Estimates of the prevalence of androgen deficiency among men 40–70 years of age range from 12 to 45%.<sup>1</sup> Approximately 481 000 new cases of androgen deficiency are diagnosed per year in the United States.<sup>1</sup>

The clinical spectrum of hypogonadism includes diminished erectile quality and sexual interest, decreased lean body mass, impaired muscle strength and reduced bone mineral density. These specific clinical symptoms and signs in association with low serum testosterone levels, validate the diagnosis which is often termed 'androgen deficiency in the aging male.'

Concurrent with mounting epidemiologic evidence that hypogonadism is more common than once thought, testosterone replacement therapy (TRT) has become an increasingly widespread practice.<sup>2</sup> In 2005, over 2.3 million prescriptions were written for men as part of testosterone replacement programs.<sup>3</sup> The benefits and safety of TRT are becoming well-established. Several recent studies have consistently demonstrated significant improvements in hypogonadal symptoms concurrently with normalization of

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serum testosterone levels.<sup>4–7</sup> Various forms of testosterone replacements exist, including intramuscular injections, oral and buccal preparations, as well as transdermal patches and gels.

Once-daily testosterone gel preparations (Testim or AndroGel) represent an effective method of hormonal replacement with an acceptable safety profile.<sup>4–7</sup> Approximately two-thirds of men on TRT use gel preparations. Occasionally, hypogonadal symptoms and/or serum testosterone levels fail to improve with the initial testosterone gel selection. Moreover, patients may experience adverse side effects necessitating testosterone gel brand substitution. The primary objective of the current study was to evaluate the efficacy of changing testosterone gel preparations among suboptimally responsive hypogonadal men.

## Materials and methods

Between 2003 and 2006, the records of all men treated with testosterone gel replacement therapy (Testim or AndroGel) for significant hypogonadal symptoms and low serum testosterone levels were reviewed to identify patients who underwent a brand change during testosterone gel treatment. Institutional Review Board approval was obtained prior to initiating the study. Indications for changing a specific testosterone gel included a suboptimal clinical or biochemical response to hormone replacement, adverse side effects or patient preference. Consistent with the Endocrine Society's guidelines, total testosterone levels were considered subtherapeutic when  $<300 \text{ ng dl}^{-1}$ .<sup>8</sup> Testosterone gel preparation changes were made at approximately equivalent dosing for each brand. All patients were initially treated with 5 g of testosterone gel. Among the patients who tolerated the gel, but failed to achieve satisfactory symptomatic or biochemical improvements, dose escalation to 10 g was considered. Patients experiencing adverse side effects associated with a particular gel were switched to the alternative gel without prior dose modification. Irrespective of dosing prior to gel substitution, all patients were changed to 5 g of the alternative gel. At the time of the study, Testim and AndroGel were the only FDA-approved gels for TRT in the United States. While using AndroGel, patients were instructed to apply the gel to the upper arms, shoulders and abdomen. While using Testim, patients were instructed to apply the gel to the upper arms and shoulders.

Prior to initiation of TRT, a complete medical and sexual history, physical examination including digital rectal examination and hormonal evaluation were performed in all men. Hormonal evaluation included measurement of free and total serum testosterone, estradiol, prostate-specific antigen, as well as hemoglobin and hematocrit levels. All

hormones were analyzed in a single laboratory (The Laboratory for Male Reproductive Research and Testing at the Baylor College of Medicine). Total testosterone measurements were performed using the Beckman AccessII platform assay. Validated normal ranges for men using this assay are  $200\text{--}1000 \text{ ng dl}^{-1}$ . Free testosterone measurements were performed using the Siemens Medical Diagnostics (Los Angeles, CA, USA) kit #TFTK1. Normal ranges for this assay are  $19\text{--}26 \text{ pg ml}^{-1}$ .

Follow-up evaluations were arranged 4 weeks after the initiation of TRT and every 6 months thereafter, once hypogonadal symptoms improved and hormone levels stabilized. At each follow-up visit, responses to components in the androgen deficiency in the aging male<sup>9</sup> questionnaire were reviewed, and digital rectal examination status and hormonal profiles were updated.

Total and free serum testosterone, hemoglobin, hematocrit, prostate-specific antigen levels and the presence and severity of hypogonadal symptoms (libido, energy levels and erectile function) were compared at baseline (day 0 of change) and 4 weeks following gel substitution for each form of testosterone therapy.

Statistical analysis was performed using SPSS statistical software.<sup>10</sup> Paired *t*-tests were used to compare changes in hormonal profiles before and after testosterone gel substitution.  $\chi^2$  testing was used to evaluate categorical variables.

## Results

Of the 370 hypogonadal men identified on testosterone gel replacement therapy, the proportion of patients using AndroGel or Testim was 71 and 29%, respectively. Among these men, 75 (20%) underwent a brand change in testosterone gel treatment.

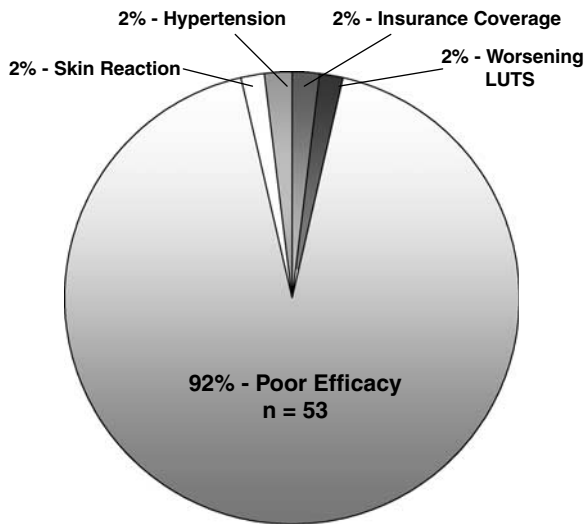
The proportion of patients initially treated with 5 or 10 g of testosterone gel and the corresponding mean total testosterone levels are summarized in Table 1.

### *Changing from AndroGel to Testim*

Eighty-three percent of men ( $n=62$ ) with a mean age of 60 years, switched from AndroGel to Testim. The predominant indication for gel substitution was poor symptomatic or biochemical efficacy

**Table 1** Testosterone gel dosing prior to substitution among study patients

	5 g	10 g
AndroGel (mean testosterone)	63% ( $317 \text{ ng dl}^{-1}$ )	37% ( $330 \text{ ng dl}^{-1}$ )
Testim (mean testosterone)	85% ( $450 \text{ ng dl}^{-1}$ )	15% ( $872 \text{ ng dl}^{-1}$ )



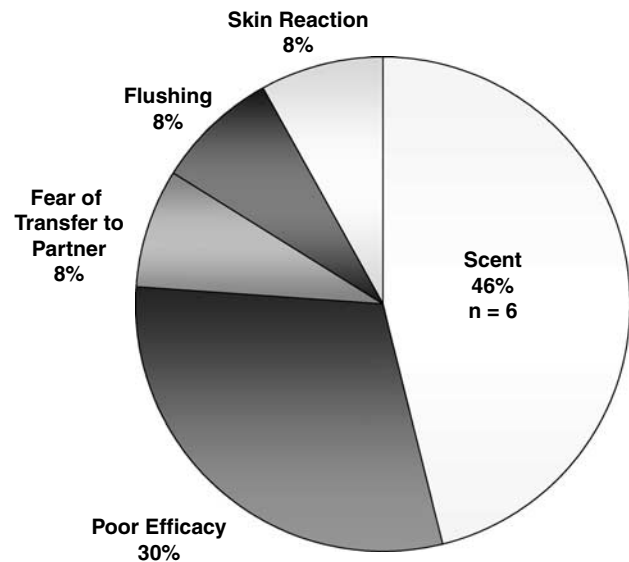
**Figure 1** Clinical indications for substituting Testim for Androge.

(Figure 1). Prior to gel substitution, among patients initially treated with Androge, the mean total and free testosterone levels were  $311 \text{ ng dl}^{-1}$  and  $10.4 \text{ pg ml}^{-1}$ , respectively. Total testosterone levels were below  $300 \text{ ng dl}^{-1}$  in 58% of these patients. Following a change to Testim, mean total and free testosterone levels increased to  $484 \text{ ng dl}^{-1}$  ( $P < 0.001$ ) and  $14.6 \text{ pg ml}^{-1}$  ( $P = 0.01$ ), respectively (Figure 3). Total testosterone levels remained below  $300 \text{ ng dl}^{-1}$  in only 17% of these patients.

#### Changing from Testim to Androge

Seventeen percent of men ( $n = 13$ ) with a mean age of 52 years, switched from Testim to Androge. The main indication for gel substitution was secondary to specific properties (scent) of Testim gel (Figure 2). Among patients initially treated with Testim, the mean total and free testosterone levels were  $544 \text{ ng dl}^{-1}$  and  $18.0 \text{ pg ml}^{-1}$ , respectively. Total testosterone levels were below  $300 \text{ ng dl}^{-1}$  in 15% of men ( $P = 0.005$ ). Following testosterone gel change to Androge, mean total and free testosterone levels were  $522 \text{ ng dl}^{-1}$  ( $P = 0.7$ ) and  $16.1 \text{ pg ml}^{-1}$  ( $P = 0.6$ ), respectively (Figure 4). Total testosterone levels remained below  $300 \text{ ng dl}^{-1}$  in 27% of these patients.

Collectively among all study patients, 14% did not appear to absorb either gel as evidenced by total testosterone levels  $< 300 \text{ ng dl}^{-1}$  pre- and post-gel substitution regardless of the direction of the switch. Improvements in hypogonadal symptoms (libido, erectile function and energy) following testosterone gel substitution for each brand are reported in Table 2. Mean prostate-specific antigen ( $0.83 \text{ ng ml}^{-1}$  pre-switch,  $0.74 \text{ ng ml}^{-1}$  post-switch) and hematocrit levels (46.9% pre-switch, 45.3% post-switch)



**Figure 2** Clinical indications for substituting Androge for Testim.

**Table 2** Improvements in hypogonadal symptoms following testosterone gel substitution.

	Libido(%)	Erectile function(%)	Energy levels(%)
Androge to Testim	69	58	65
Testim to Androge	46	39	46

did not change significantly from baseline following gel substitution with either product.

## Discussion

Testosterone replacement among hypogonadal men using testosterone gel formulations has been shown to normalize and maintain serum testosterone levels at a steady state.<sup>5,6,11</sup> Concurrent with beneficial biochemical changes, significant improvements in sexual motivation, spontaneous erections, lean body mass, fat distribution and bone mineral density have been reported.<sup>4-7</sup>

The primary objective of the current investigation was to evaluate the benefit of changing testosterone gel preparations among hypogonadal men who initially achieved a suboptimal clinical or biochemical response with their first gel brand. Despite the reported efficacy of testosterone gels, we found that a significant proportion of men on testosterone gel replacement therapy (20%) have a suboptimal clinical or biochemical response to initial gel selection.

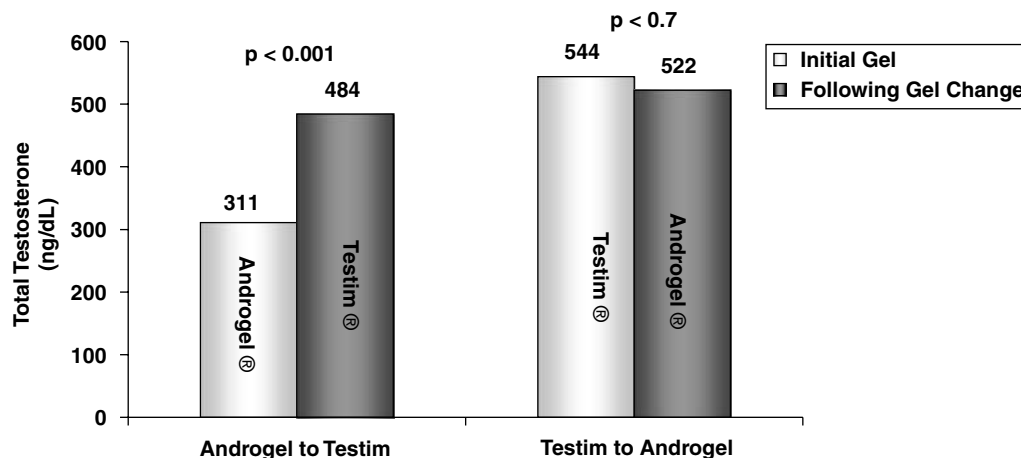


Figure 3 Total serum testosterone levels pre- and post-gel substitution.

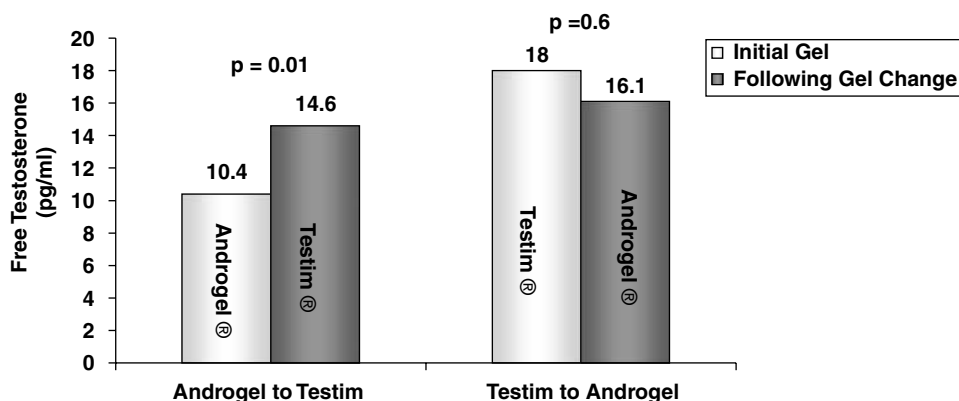


Figure 4 Free testosterone levels pre- and post-gel substitution.

Previous smaller studies have demonstrated that among patients with an initial inadequate response to Androgel, hypogonadal signs and symptoms including sex drive, erectile and ejaculatory function, cognition and overall sexual satisfaction improved significantly following a change to 1% Testim gel.<sup>12,13</sup>

The current study reports on a larger sample of hypogonadal men, with bi-directional gel substitution, using validated clinical and biochemical end points. Consistent with earlier reports, hypogonadal symptoms improved from baseline in a significant proportion of patients who underwent a brand substitution following an initial suboptimal biochemical or symptomatic response. Moreover, we found that total and free serum testosterone levels increased significantly following a switch from Androgel to Testim, but not from Testim to Androgel.

The current findings are probably explained by differing pharmacokinetics properties among the two testosterone gels. Randomized, crossover studies have demonstrated that peak serum concentrations of total testosterone, free testosterone and dihydrotestosterone are significantly greater

following dose equivalent application of Testim gel compared to Androgel.<sup>5,14</sup> The enhanced absorption of Testim is attributed to pentadecalactone, an emollient specific to Testim, which also accounts for the unique scent of the gel.<sup>14</sup>

Reflecting this underlying physiology, the majority (92%) of men switched from Androgel to Testim secondary to persistent hypogonadal symptoms or subtherapeutic serum testosterone levels. In contrast, the leading indication for substituting Androgel for Testim was not due to a subtherapeutic clinical response or poor drug absorption, but secondary to specific properties of the gel (that is scent of the gel, skin residue or reaction). Consequently, it seems reasonable to expect these men to continue to respond to the alternative gel (Androgel) following gel substitution. Consistent with this rationale, total and free serum testosterone levels were relatively maintained following a switch from Testim to Androgel (Figures 3 and 4). On the basis of our data, substituting Testim for Androgel offers hypogonadal men the potential for improved clinical and biochemical responsiveness. In contrast, an Androgel for Testim substitution is indicated in an

attempt to eliminate or minimize unwanted side effects but is less likely to offer patients significant symptomatic or biochemical improvements.

We acknowledge that because the study population was uncontrolled, absolute compliance with treatment and standardized dosing could not be assured. Moreover, while our general tendency is to obtain early-morning serum testosterone levels, on occasion the realities of a real life clinical practice prevented this ideal time for testosterone testing. Finally, the higher proportion of patients changing from AndroGel to Testim to a significant degree reflects market share trends during the course of the study as well as the researcher's earlier practice tendency of initiating testosterone gel therapy with AndroGel.

## Conclusions

A significant proportion of men on testosterone gel replacement therapy (20%) have a suboptimal response to the initial brand of testosterone gel prescribed. A change in testosterone gel preparation among initially unresponsive hypogonadal men is justified prior to abandoning or considering more invasive TRT. Changing from AndroGel to Testim offers hypogonadal men the potential for improved clinical and biochemical responsiveness. Changing from Testim to AndroGel is indicated to eliminate or minimize unwanted side effects but is less likely to offer significant biochemical improvements.

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## Conflict of interest

There are no sources of funding directly related to this research to disclose.

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