Testosterone 2% Gel Can Normalize Testosterone Concentrations in Men with Low Testosterone Regardless of Body Mass Index

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ABSTRACT

Introduction. Little is known about the effect of body mass index (BMI) on the efficacy and safety of testosterone therapy in hypogonadal men. A prior noncomparative trial demonstrated that testosterone 2% gel restored testosterone levels in hypogonadal men and was generally well tolerated.

Aim. This post hoc analysis evaluated the influence of BMI on the pharmacokinetics of testosterone therapy in men with low testosterone.

Methods. Men (N = 149) aged 18–75 applied testosterone 2% gel to the front and inner thigh once daily for 90 days. Starting dose was 40 mg/day, which could be adjusted at days 14, 35, and 60. Patients were split into categories depending on baseline BMI: Tertile 1 (≤29.1 kg/m^2), Tertile 2 (29.2–32.4 kg/m^2), and Tertile 3 (>32.4 kg/m^2).

Main Outcome Measures. Efficacy end points were average serum total testosterone concentrations over 24 hours and maximum serum testosterone concentrations at day 90. Adverse events were recorded.

Results. The efficacy analysis included 129 men with low testosterone (mean age 52.9, 54.0, and 54.2 years for Tertiles 1, 2, and 3, respectively) defined as serum testosterone <250–300 ng/dL. Baseline testosterone levels were comparable across BMI tertiles. After 90 days of treatment with testosterone 2% gel (≥40 mg/day), 79.1%, 79.5%, and 73.8% of patients in Tertiles 1, 2, and 3, respectively, achieved serum testosterone concentrations in the physiologic range (i.e., ≥ 300 to ≤ 1,140 ng/dL). The mean average daily dose at day 90 was higher in participants in Tertiles 3 vs. 2 ($P = 0.039$) and Tertiles 3 vs. 1 ($P = 0.010$). The gel was generally well tolerated, with skin reactions the most commonly reported adverse event (16.1%; n = 24).

Conclusions. In this study, daily application of testosterone 2% gel was effective at returning serum testosterone to physiologic levels in men with low testosterone and high BMI, although required dose was affected by BMI. **Dobs A, Norwood P, Potts S, Gould E, and Chitra S. Testosterone 2% gel can normalize testosterone concentrations in men with low testosterone regardless of body mass index. J Sex Med 2014;11:857–864.**

Key Words. Body Mass Index; Hypogonadism; Testosterone Replacement; Transdermal Systemic Testosterone Gel

Introduction

Male hypogonadism is a clinical syndrome characterized by a reduced concentration of serum testosterone and several signs or symptoms, including decreased libido, erectile dysfunction, increased body fat, fatigue, and anemia [1]. Testosterone levels can decrease with advancing age [2,3], which can lead to late-onset hypogonadism, a condition that has been more strongly associated with sexual symptoms (e.g., decreased morning erection frequency, decreased sexual thoughts, and erectile dysfunction) than physical or mental indicators [4]. For decades, male hypogonadism has been treated with testosterone replacement therapy (TRT), the aim of which is to restore testosterone levels to physiologic levels [5].

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Through TRT and the subsequent normalization of testosterone, many signs and symptoms of hypogonadism can be reversed.

In addition to sexual side effects, low serum testosterone concentration has been associated with a number of comorbidities, including diabetes, hypertension, hyperlipidemia, obesity, asthma/chronic obstructive pulmonary disease, rheumatoid arthritis, and prostate disease [6]. In addition, several large meta-analyses of studies conducted in hypogonadal men support the association between hypogonadism and metabolic syndrome (MetS), type 2 diabetes, and cardiovascular (CV) mortality [7–9]. MetS, defined by a constellation of components including elevated fasting glucose, increased triglycerides, decreased high-density lipoprotein, increased blood pressure, and increased waist circumference [10], is more likely to occur in men with lower testosterone levels [7,11]. Although there is no indication that TRT can reverse MetS, significant improvement in a number of metabolic parameters, including waist circumference, blood pressure, triglycerides, and fasting blood glucose, was observed after treatment [7,11]. Testosterone treatment may also be a control point for managing diabetes [9] and CV disease [8]. Type 2 diabetes has been shown to be independently associated with hypogonadism, and the restoration of physiologic testosterone levels resulted in improvements in glycemic control and potentially insulin resistance [9]. Hypogonadism is also associated with increased CV morbidity and mortality, with TRT resulting in improved exercise capacity [8]. Improvements in total cholesterol [12] and bone mineral density [12–14], as well as the prevention of age-related changes in body mass index (BMI) and fat content, have been demonstrated with TRT in hypogonadal men [15].

Excess weight is a contributing factor for a variety of diseases, including MetS, type 2 diabetes, and CV disease [16]. The influence of weight on testosterone levels was examined in a meta-analysis focused on obese men with hypogonadism. Results indicated that weight loss was the best predictor for increasing testosterone levels without pharmacologic intervention; moreover, greater decreases in BMI were associated with higher testosterone increases [17]. At present, there is limited knowledge about how body weight may affect the efficacy or dosing of TRT in hypogonadal men. The existing evidence for an association is mostly indirect. Findings from one study suggest that symptom improvements with testosterone therapy were less marked in patients with depression and that, in this study, patients with depression were more obese [18]. In adult men, testosterone levels have been shown to be negatively correlated with BMI [19,20], and obesity is a common comorbidity for men with hypogonadism [6,21]. Although BMI may influence endogenous testosterone levels, it is unclear whether BMI has any affect on the serum level of testosterone attained with TRT.

A 2007–2008 phase III trial revealed that the application of testosterone 2% gel (Fortesta Gel; Endo Pharmaceuticals Inc., Malvern, PA, USA) normalized testosterone levels in male patients with low testosterone undergoing TRT (NCT00522431) [22]. This post hoc analysis from this trial was subsequently completed to determine the influence of baseline BMI on dosage requirement and serum testosterone levels in the population analyzed in that trial.

Aims

The aim of this study is to determine TRT dosage requirements, maximum testosterone concentration after 90 days, and adverse events (AEs) in men with low testosterone treated with 2% testosterone gel and stratified by BMI.

Methods

The study on which this post hoc analysis is based was a multicenter, open-label, noncomparative trial in men with low testosterone that lasted 90 days. The methodology, baseline characteristics of the total population, and major outcomes of the main study have been previously detailed [22]. Details of the phase III trial methodology relevant to this post hoc analysis are provided in brief.

Patients and Study Design

Men aged 18–75 years with low testosterone (defined as a single serum total testosterone concentration <250 ng/dL or two consecutive serum total testosterone concentrations <300 ng/dL at least 1 week apart) were considered for the phase III trial. Most clinicians and various medical society guidelines recommend that the disease state of hypogonadism be defined as both low serum testosterone levels and symptoms. For the purposes of this study, where testosterone was only administered for a short period of time, the dose requirements were determined simply based on whether a man had low hormone levels. To be eligible for inclusion, patients had to have a BMI of ≥22 to <35 kg/m^2. The use of stable doses of