Testosterone with Dutasteride, but Not Anastrazole, Improves Insulin Sensitivity in Young Obese Men: A Randomized Controlled Trial

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ABSTRACT

Introduction. Testosterone (T) administration to men increases T, estradiol (E2), dihydrotestosterone (DHT), and fat-free mass (FFM), and decreases fat mass (FM) but does not consistently improve insulin sensitivity (IS).

Aim. The aim of this study was to examine the effects of T administration in obese, nondiabetic men on body composition and IS, and to determine if inhibition (i) of metabolism of T to E2 with anastrazole or to DHT with dutasteride alters these effects.

Methods. This was a 98-day randomized, double-blind, parallel group, placebo-controlled trial of 57 men, 24–51 year, free T in the lower 25% of normal range (<0.33 nmol/L), body mass index ≥30.0 kg/m^2. Subjects were randomized to one of four groups: (i) *placebo*: gel, pills, and injection; (ii) *T/DHT/iE2*: T gel, anastrazole, and acyline (gonadotropin releasing-hormone antagonist to suppress endogenous T); (iii) *T/iDHT/E2*: T gel, dutasteride, and acyline; (iv) *T/DHT/E2*: T gel, placebo pills, and acyline.

Main Outcome Measures. Main outcome measures are insulin sensitivity as percent change (%Δ) in glucose disposal rates (GDR) from a two-step euglycemic clamp (GDR1 and 2), and %FM and %FFM by dual X-ray absorptiometry scan.

Results. *Insulin Sensitivity:* %Δ GDR1 differed across groups ($P = 0.02$, ANOVA) and was significantly higher in the dutasteride (T/iDHT/E2) compared with the placebo and T gel (T/DHT/E2) groups. %ΔGDR2 was higher in the dutasteride (T/iDHT/E2) compared with the anastrazole (T/DHT/iE2) group. *Body Composition:* T gel alone (T/DHT/E2) or with dutasteride (T/iDHT/E2) significantly increased %FFM ($P < 0.05$) and decreased %FM ($P < 0.05$). There was no change in %FFM or %FM after placebo or anastrazole (T/DHT/iE2).

Conclusions. The combination of T plus dutasteride improved body composition and IS while T alone improved body composition but not IS, suggesting that when T is administered to men, reduction to DHT attenuates the beneficial effects of aromatization to E2 on IS but not body composition. **Juang PS, Peng S, Allehmazedeh K, Shah A, Coviello AD, and Herbst KL. Testosterone with dutasteride, but not anastrazole, improves insulin sensitivity in young obese men: A randomized controlled trial. J Sex Med 2014;11:563–573.**

Key Words. Testosterone; Obesity; Insulin Sensitivity; Aromatase; 5-alpha Reductase; Dihydrotestosterone

Introduction

Obesity is prevalent worldwide and in men, is associated inversely with free testosterone (T) levels [1]. T administration increases muscle and decreases fat [2,3], but while skeletal muscle is the main site for insulin-stimulated glucose disposal in the body [4], many studies examining effects of T administration in men do not suggest a consistent pattern of improved insulin sensitivity (IS) [5].

When T is administered to men, aromatase converts T to estradiol (E2) and 5α-reductase isoenzymes 1 and 2 convert T to dihydrotestosterone

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(DHT), a potent androgen, thereby raising all three hormones (T/E2/DHT). The effects of E2 and DHT on IS and body composition in men are relatively unknown. Lower E2 levels increase visceral fat in men [6] and increase fat and insulin levels in rodents [7] while higher levels of E2 are more potent than T at feedback inhibition (i) of gonadotropins [8]. Estrogen receptor alpha knockout mice have decreased hepatic IS [9] suggesting that E2 is beneficial for IS. Epidemiologic studies have shown however that increased E2 and decreased T levels are associated with cardiovascular disease (CVD) [10]. Yet, observational data in men in the Framingham Heart Study have shown that higher levels of the less potent estrogen estrone (E1) predict development of diabetes in men, while higher levels of E2 levels do not [11]. Thus, the role of estrogens in metabolism and IS in men remains unclear.

Although effects of DHT on obesity and IS are unclear, one study found an association between increased 5α-reductase activity and decreased IS [12], suggesting that DHT in men attenuates the effects of E2. Use of DHT gel in middle-aged men with abdominal obesity had no effect on IS [6], and a recent study demonstrated that the conversion of T to DHT was not essential for mediating its anabolic effects on muscle [13]. DHT gel has also been shown to reduce fat mass (FM) and improve some measures of muscle strength [14].

Aim

The aim of this study was to determine if T administration in young, obese men improved body composition and IS, and if inhibiting metabolism of T to E2 or DHT would change these outcomes. We hypothesized improvements in fat-free mass (FFM), FM, and IS after T administration would be attenuated by the aromatase inhibitor, anastrazole (increased T and DHT, inhibition of conversion to E2 [T/DHT/iE2]), and enhanced by the dual isoenzyme, 5α-reductase inhibitor, dutasteride (increased T and E2, inhibition of reduction to DHT [T/iDHT/E2]).

Methods

Study Design

Prospective, randomized, double-blind, parallel group, placebo-controlled clinical trial for 98 days (D98) approved by Institutional Review Boards at Charles R. Drew (Drew) University of Medicine and Science (Los Angeles, CA), the University of California, San Diego (UCSD), and by the VA San Diego Healthcare System (VASDHS) Research and Development Committee. All men gave consent prior to participation. Study visits occurred between December 20, 2004 to July 9, 2009 at the Center for Metabolic Research at the VASDHS and the UCSD General Clinical Research Center (GCRC), except for the first eight subjects who completed visits at Drew's GCRC (ClinicalTrials.gov number NCT00983554).

Inclusion and Exclusion Criteria

Inclusion criteria: The criteria are (i) healthy men, age 21–50 years; (ii) free T level in the lower 25% of the normal range or below; (iii) body mass index (BMI) >30 kg/m^2; (iv) ambulatory and medically stable; and (v) able to give informed consent and comply with the protocol. **Exclusion criteria**: The criteria are (i) disorders known to cause or be associated with hypogonadism, e.g., pituitary tumors, hyperprolactinemia, human immunodeficiency virus (HIV) infection, Klinefelter's syndrome, or Kallman's syndrome; (ii) uncontrolled hypertension, diabetes, congestive heart failure, or chronic lung disease; (iii) alcohol or drug dependence currently or in the preceding 6 months as identified by the Alcohol Use Disorders Test (AUDIT) questionnaire score >8 [15]; (iv) disorders that might be exacerbated by androgen treatment (e.g., benign prostatic hyperplasia [BPH] with an American Urological Association [AUA] symptom score >14 [16] or prostate cancer), erythrocytosis (hematocrit >48% at baseline), or sleep apnea assessed by Berlin's questionnaire [17]; (v) serum prostate-specific antigen (PSA) >4 μg/L; (vi) serum alanine transferase, aspartate transferase (AST), alkaline phosphatase elevation greater than three times the upper limit of normal; (vii) creatinine greater than 2 mg/dL; (viii) the use of medications that might affect muscle or bone metabolism (glucocorticoid, recombinant human growth hormone, androgenic steroids, oral androgen precursors such as androstenedione or dihydroepiandrostenedione), or androgen metabolism, action, or clearance (dilantin, phenobarbitol, aldactone, flutamide, finasteride); and (ix) class III or IV congestive heart failure, myocardial infarction, or acute coronary event in the preceding 6 months. Participants who met enrollment criteria were randomized to groups matched for age and BMI according to randomization tables with a block size of 6.