Psychoneuroendocrinology 72 (2016) 63–71

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Testosterone and depressive symptoms among men in the Diabetes Prevention Program

Catherine Kim[a,*], Elizabeth Barrett-Connor[b], Vanita R. Aroda[c], Kieren J. Mather[d], Costas A. Christophi[e], Edward S. Horton[f], Xavier Pi-Sunyer[g], George A. Bray[h], Fernand Labrie[i], Sherita Hill Golden[j], on behalf of the Diabetes Prevention Program Research Group

[a] University of Michigan, Ann Arbor, MI, United States
[b] University of California San Diego, La Jolla, CA, United States
[c] MedStar Health Research Institute, Hyattsville, MD, United States
[d] Indiana University, Indianapolis, IN, United States
[e] George Washington University, Rockville, MD, United States
[f] Joslin Diabetes Center, Boston, MA, United States
[g] Columbia University, New York City, NY, United States
[h] Louisiana State University, Baton Rouge, LA, United States
[i] Endoceutics, Quebec, Canada
[j] Johns Hopkins University, Baltimore, MD, United States

ARTICLE INFO

Article history:
Received 13 April 2016
Received in revised form 12 June 2016
Accepted 13 June 2016

Keywords:
Testosterone
Androgens
Mood
Glucose-intolerance

ABSTRACT

Objective: We examined associations between intensive lifestyle intervention (ILS) and changes in testosterone and associations with mood among middle-aged men.
Design: Secondary analysis of men (n = 886) participating in the Diabetes Prevention Program which randomized glucose-intolerant, overweight men to ILS, metformin, or placebo between 1996 and 1999.
Main outcome measures: Changes in testosterone between baseline and 1-year follow-up asnd associations of these changes with mood measures (Beck Depression Inventory [BDI-II], Beck Anxiety Inventory [BAI]).
Results: Median baseline testosterone was 10.98 nmol/l and 44% (n = 385) had testosterone < 10.41 nmol/l or 300 ng/dl. Testosterone increases were greater among men randomized to ILS vs. metformin vs. placebo (1.15 nmol/l vs. −0.12 nmol/l vs. −0.27 nmol/l, p < 0.001). The association between changes in testosterone and mood differed by study arm (p < 0.001 for interaction); there were no significant associations between changes in testosterone and mood changes among men in the ILS or placebo arms. Among men in the metformin arm, increases in testosterone were significantly associated with decreases in BDI-II (improved depressive symptoms) (β-coefficient −0.2336, p = 0.0002) indicating a 0.23 decrease in BDI-II for every 1 nmol/l increase in testosterone and decreases in BAI (improved anxiety symptoms) (β-coefficient −0.2147, p = 0.0014). Similar patterns were observed for bioavailable testosterone.
Conclusions: Among overweight middle-aged men with glucose-intolerance, ILS increased endogenous testosterone slightly but without significant improvements in mood. Metformin did not increase testosterone, but among metformin users, testosterone increases were associated with improvements in mood. Thus, interventions that increase endogenous testosterone may not also improve mood.

1. Introduction

1.1. Studies regarding the association between mood and testosterone in middle-aged and younger men conflict. It is unclear how much advancing age and increasing weight confound the association

Among older men, low testosterone concentrations are associated with depressed mood (Almeida et al., 2008; Barrett-Connor

* Corresponding author at: 2800 Plymouth Road, Building 16, Room 430W, Ann Arbor, MI 48109-5429, United States.
E-mail addresses: cathkim@umich.edu, cathkim@med.umich.edu (C. Kim).

http://dx.doi.org/10.1016/j.psyneuen.2016.06.009
0306-4530/

et al., 1999; Berglund et al., 2011; Morsink et al., 2007) and with incident depression (Almeida et al., 2008; Ford et al., 2016; Joshi et al., 2010; Shores et al., 2005). However, studies in younger men conflict, reporting associations between lower testosterone and depression (McIntyre et al., 2006), no association (Travison et al., 2007), or associations only among men with specific androgen receptor morphology(Colangelo et al., 2007). Thus, the extent to which testosterone is associated with mood independent of advancing age is not clear. On average, testosterone levels decline by approximately 0.8% per year beginning in middle-age, so that a man with a baseline value of 17.35 nmol/l (500 ng/dl) could have a decline of about 0.69–0.87 nmol/l (4–5 ng/dl) per year (Orwoll et al., 2006). Moreover, comorbidities, particularly obesity, are strongly associated with reduced testosterone concentrations (Shi et al., 2013; Travison et al., 2007). In turn, older age (Zhao et al., 2012) and greater weight (Luppino et al., 2010) are associated with increased risk of depression.

1.2. No randomized trials examine whether interventions which increase endogenous testosterone also improve mood

Observational studies suggest that overweight and obese men who undergo lifestyle modification experience increases in testosterone (Camacho et al., 2013; Hall et al., 2008; Kumagai et al., 2015; Mohr et al., 2006; Travison et al., 2007; Zmuda et al., 1997). One small study (n = 40) noted that lifestyle intervention increased testosterone in frail elders (Armamento-Villareal et al., 2016). However, no randomized trials have examined whether lifestyle changes result in endogenous testosterone changes, and whether subsequent increases have beneficial effects upon mood. To our knowledge, no trials in men have examined whether testosterone levels change with metformin. Several observational studies suggest that metformin decreases testosterone levels along with weight (Ozata et al., 2001; Shegem et al., 2002), although another small observational study noted that testosterone increased after implementation of modifications to diet and increases in physical activity (Casulari et al., 2010). Other antidiabetic medications such as pioglitazone have been reported to decrease total and bioavailable testosterone even with significant weight loss (Sridhar et al., 2013).

1.3. The Diabetes Prevention Program was a trial which assessed changes in endogenous testosterone and mood as secondary outcomes in middle-aged men

The Diabetes Prevention Program (DPP) was a randomized clinical trial which assigned overweight, glucose-intolerant individuals to intensive lifestyle intervention (ILS) vs. metformin vs. placebo with the goal of diabetes delay or prevention (Knowler et al., 2002). Participants were randomized 1996–1999. The DPP measured androgen levels at baseline and at one-year follow-up and concurrently assessed mood, anti-depressant medication use, and weight. The majority of men were less than 65 years of age at baseline. Approximately 55% had total testosterone concentrations greater than 10.41 nmol/l (300 ng/dl) (Mather et al., 2015), a cut point commonly used to define hypogonadism in younger men, along with other criteria of symptoms and signs of hypogonadism (Bhasin et al., 2010). Of note, there is not a consensus regarding the optimal cut point. Previous DPP reports have noted that participants reported a decline in depressive symptoms over the course of the study, largely attributable to the concurrent trend of increased anti-depressant medication use, but also due to weight loss (Rubin et al., 2005). Although study arm did not impact prevalence of depression, weight loss was significantly associated with lower prevalence of depression and medication use. Building upon these previous results, we examined whether testosterone itself was affected by lifestyle intervention or metformin, whether any observed changes in testosterone were due to changes in weight, and whether testosterone changes (regardless of study arm) were associated with mood.

1.4. Objectives and hypotheses

Specifically, we addressed the following questions: (1) does randomization to a lifestyle intervention targeting weight loss or randomization to metformin alter testosterone compared to placebo among mid-life men, (2) are changes in endogenous testosterone associated with changes in mood in mid-life men, independent of age, race/ethnicity, weight, and anti-depressant medication use, (3) are changes in testosterone associated with mood changes in a cohort with a wide range of testosterone levels? We hypothesized that testosterone would increase among men randomized to lifestyle change and metformin; such increases would be associated with improved mood; and such changes would be most marked among men who had low levels of testosterone at baseline.

2. Materials and methods

2.1. Setting and population

The DPP study population has been previously described (Knowler et al., 2002). The eligibility criteria included age at least 25 years, BMI at least 24 kg/m^2 (22 kg/m^2 in people of Asian descent), fasting plasma glucose 95–125 mg/dl, and glucose 2 h after a 75-g oral glucose load of 140–199 mg/dl. All participants provided written informed consent, and each participating institution was overseen by its own ethics review board. Eligible participants were randomly assigned to one of three interventions: 850 mg metformin twice daily, placebo twice daily, or ILS. The goals of ILS were to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet plus moderate physical activity for at least 150 min per week. Weight and waist circumference were measured semiannually. Participants included in this report approved the use of their blood samples for secondary analyses. This cohort included male DPP participants with pre-randomization blood samples and blood samples at one year follow-up that were available for steroid sex hormone assays (Fig. 1) and who did not report exogenous sex steroid use. We excluded one participant with a large increase in testosterone concentrations suggesting unreported hormone use, on the order of 34 nmol/l, (~1000 ng/dl) for a total of 886 participants.

2.2. Testosterone and SHBG measurements

As previously described, (Mather et al., 2015) sex steroids were measured using gas chromatography/mass spectrometry. The lower limits of quantification for testosterone was 0.1735 nmol/l. Interassay variation (coefficient of variation) at the lower limit of quantification for testosterone was 10.7%. Values were extrapolated below the lower limit of quantitation using Mass Hunter Workstation software (Agilent, Santa Clara, CA). Sex hormone binding globulin (SHBG) was assessed using an ELISA (Bioline) with interassay coefficients of variation of 7.8% and 5.0% at 18.2 and 63.1 nmol/l, respectively.

2.3. Mood assessments

Participants completed the Beck Depression Inventory (BDI-II) prior to randomization and at each annual visit (Beck et al., 1996). The BDI-II is a 21-item depression severity scale for adults. Higher