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Glucose Ingestion does not lower Testosterone concentrations in men on Testosterone Therapy

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Conflict of Interest/Disclosure summary

Dr. Dhindsa has received honoraria from Bayer, Acerus Pharmaceuticals and Marius pharmaceuticals, and research support from Clarus Therapeutics. Dr. Dandona has received honoraria from Eli Lilly, Novartis, GlaxoSmithKline, Merck, Novo Nordisk, Takeda and Sanofi- Aventis, and research support from National Institutes of Health, JDRF, ADA, Novo Nordisk, Bristol Meyer Squibb, AbbVie Pharmaceuticals, Astra Zeneca and Boehringer Ingelheim Pharmaceuticals. These interests are not related to and did not influence the current study. All other authors declare no competing financial interests.

Abstract

Oral calorie intake causes an acute and transient decline in serum testosterone concentrations. It is not known whether this decline occurs in men on testosterone therapy. In this study, we evaluated the change in testosterone concentrations following oral glucose ingestion in hypogonadal men before and after treatment with testosterone therapy. This is a secondary analysis of samples previously collected from a study of hypogonadal men with type 2 diabetes who received testosterone therapy. Study participants (n=14) ingested 75 grams of oral glucose and blood samples were collected over two hours. The test was repeated after 23 weeks of intramuscular testosterone therapy. The mean age and BMI of study volunteers were 53±8 years and 38±7 kg/m^2 respectively. Following glucose intake, testosterone concentrations fell significantly prior to testosterone therapy (week 0, *P*=0.04). The nadir of testosterone concentration was at one hour, followed by recovery to baseline by two hours. In contrast, there was no change in testosterone concentrations at week 23. The change in serum testosterone concentrations at 60 minutes was significantly more at week 0 than week 23 (-11±10% versus 0±16%, *P*=0.05). We conclude that oral glucose intake has no impact on testosterone concentrations in men on testosterone therapy. Endocrinology societies should consider clarifying in their recommendations that fasting testosterone concentrations are required for diagnosis of hypogonadism, but not for monitoring testosterone therapy.

Oral calorie intake causes an acute and transient decline in serum testosterone concentrations (1). This fall in testosterone is usually evident within 20 minutes of the food intake, plateaus in 60 minutes and recovers by 4 hours (1). This phenomenon has been observed after any type of macronutrient intake (glucose, fat, protein) (1-3). In contrast, testosterone concentrations do not change acutely after ingestion of water, in the absence of food intake. Sex hormone binding globulin (SHBG) concentrations do not change in the short term after meal intake (2, 4). Therefore, free and bioavailable testosterone concentrations also decline. The mechanism of this decline in testosterone following a meal is not known. Two possibilities are 1) reduction in synthesis or secretion of testosterone, and 2) increased metabolism/clearance/tissue uptake of testosterone. If the former is true, then the decline in testosterone concentrations would not be observed in hypogonadal men on exogenous testosterone replacement. If the latter is true, then the decline would be observed regardless of whether the serum testosterone is produced endogenously or derived from an exogenous source.

Endocrine Society guidelines recommend that testosterone measurements in men should be performed in a fasting state (5). It is not known whether this recommendation applies to men on testosterone therapy as well. We evaluated the change in testosterone concentrations following oral glucose ingestion in hypogonadal men before and after treatment with testosterone therapy.

Methods

This is a secondary analysis of samples previously collected from a study of hypogonadal men with type 2 diabetes who received testosterone therapy for 23 weeks (Diabetes Care. 2016 Jan;39(1):82-91). Briefly, the primary trial included 44 men with hypogonadotropic hypogonadism and type 2 diabetes between the ages of 30-65 years. They were randomized to receive intramuscular injections of testosterone (therapy initiated with 200mg) or placebo (saline 1ml) every 2 weeks for 23 weeks. The

dose of testosterone was adjusted to keep serum free testosterone concentrations in the mid-normal range. The study was designed to evaluate the metabolic aspects of testosterone replacement in men with obesity associated hypogonadism. The details on study design as well as the results on insulin sensitivity, inflammation and body composition have previously been published (6). Hypogonadotropic hypogonadism was defined as subnormal free testosterone concentration (<5 ng/dl) on two occasions along with low or normal LH concentrations. Men with known organic causes of hypogonadism such as panhypopituitarism, congenital HH, prolactinoma or severe head trauma were excluded from the study. Study participants ingested 75 grams of oral glucose and blood samples were collected at 0, 30, 60, 90 and 120 minutes. The test was repeated after 23 weeks of intramuscular testosterone therapy. The study volunteers received a testosterone injection at 21 weeks. For the purposes of this secondary study, we included 14 men who received testosterone therapy, underwent oral glucose intake experiment at baseline and 23 weeks, and had sufficient sera available for analysis.

The protocol was approved by the Human Research Board of the State University of New York at Buffalo, informed consent was signed by all subjects and the trial was registered with clinicaltrials.gov (NCT01127659)

Total testosterone concentrations were measured by liquid chromatography tandem mass spectrometry. (Quest Diagnostics Nichols Institute, Valencia, CA) (7).

Group comparisons were performed by two-sided *t* tests and Mann-Whitney rank sum tests as appropriate. Percent change from baseline was calculated and statistical analysis for change from baseline was carried out using *t*-test or one-way repeated measures analysis of variance (ANOVA) followed by Dunn's post hoc multiple comparison test by SigmaPlot V 11 software (Systat Software Inc., Palo Alto, CA). Pearson correlation was used to study the relationship between two variables. Data are presented as means ± standard deviation, except for the graphs which show means ± standard error.

P<0.05 was considered significant. The primary endpoint of this analysis was to compare the percent change in testosterone concentrations from 0 to 60 minutes prior to (0 week) and after testosterone therapy (23 weeks). Comparisons were made with *t* tests. The difference is shown as mean difference [25th, 75th percentile].

Results

The mean age and BMI of study participants were 53±8 years and 38±7 kg/m^2 respectively. Mean total and free testosterone concentrations at baseline (week 0) were 264±97 ng/dl and 3.9±1.2 ng/dl. The serum total and free testosterone concentrations at week 22 (one week after testosterone injection) were 510±209 ng/dl and 10.9±5.6 ng/dl. At week 23 (the day of oral glucose experiment), the mean total testosterone concentration was 376±211 ng/dL. Figure 1 shows that total testosterone concentrations following oral glucose intake at weeks 0 and 23. Figure 2 shows the percentage change in testosterone concentrations following glucose intake at weeks 0 and 23. The testosterone concentrations fell significantly at week 0 (*P*=0.04 by ANOVA). The nadir of testosterone concentration was at one hour, followed by recovery to baseline by two hours. In contrast, there was no change in testosterone concentrations at week 23 (*P*= 0.98 by ANOVA). The change in serum testosterone concentrations at 60 minutes was significantly more at week 0 than week 23 (-11±10% versus 0±16%, mean difference -10.5 [-0.49, -20.6], *P*=0.05).

The change in testosterone concentrations at 60 minutes was related to BMI (r=0.59, p=0.03) at week 0, i.e., more obese men had a smaller fall in testosterone. The change in testosterone at 60 minutes was not related to age (r= -0.05, p=0.87) or baseline testosterone concentrations (r= -0.29, p=0.35) at week 0.

Discussion

Our study clearly show that oral glucose intake has no impact on testosterone concentrations in men on testosterone therapy. Therefore, it is not necessary to obtain a fasting blood sample to monitor testosterone concentrations in men on testosterone therapy.

It has been well documented that serum testosterone concentrations fall acutely and transiently after calorie intake (1-4, 8). While the mechanism is not known, the decline could be due to either decreased secretion or increased clearance of testosterone from the blood postprandially. Our data provide conclusive evidence against the latter. If the post prandial decline in testosterone was related to increased clearance or metabolism, there should be a fall in serum testosterone regardless of whether testosterone was produced endogenously or supplied exogenously. In the presence of adequate testosterone therapy, endogenous testosterone secretion is minimal to none. Since there was no change in testosterone concentrations after oral glucose intake in men taking testosterone therapy in our study, it seems that the cause of post-prandial decline in testosterone is decreased synthesis or secretion of testosterone.

As previously mentioned, SHBG does not change acutely after meal intake (2, 4, 9). Estradiol also does not change (10). If the decline in testosterone following a meal was related to a decrease in SHBG or enhanced conversion to estradiol, it would have a similar impact regardless of whether the testosterone was endogenous or provided from an external source. Thus, our study provides corroborative evidence against these mechanisms.

Ours is also the first study to have evaluated the change in testosterone in untreated hypogonadal men. Previous studies have studied the meal induced decline in testosterone in healthy men. Some studies have included men with comorbidities which are associated with a high prevalence of hypogonadism, such as diabetes or lung disease (11, 12). However, no study had previously investigated a group of

hypogonadal men. We found that testosterone concentrations declined by 11% after oral glucose ingestion in hypogonadal men. This is somewhat less than the decline previously reported in eugonadal men (11-34%) following glucose intake (1, 9). This may be because of a lower baseline testosterone in hypogonadal men, and/or limited ability of their gonadal axis to be modulated by physiologic challenges. Interestingly, we found that higher BMI was associated with a lesser postprandial decline in testosterone concentrations. It is well known that obesity has a suppressive effect on the gonadal axis (13). It also appears that obesity impacts the response of gonadal axis to meal intake. Our data are partly consistent with a prior study which showed that elderly and obese men had a smaller decline in testosterone after mixed meal consumption as compared to younger and lean men (8).

It is not clear how meal intake reduces secretion of testosterone, and whether the effect is centrally mediated or by a direct effect on testicular production. Prior studies have not shown a consistent effect on gonadotropins. In one study, LH pulses were little lower, but mean LH was not affected (14). Other studies have found an increase (12), decrease (15) or no change in LH concentrations in the post prandial setting (1, 2, 4, 9, 10, 16). Prolactin either decreases or does not change after macronutrient intake (1). A small rise in cortisol concentrations has occasionally been observed after meal intake (17). In one study, testosterone declined but cortisol did not change after glucose ingestion (9). No relation has been noticed between the post prandial decline in testosterone and changes in glucose, insulin, leptin, or adiponectin (8, 9, 14, 16).

We and others have shown that macronutrient intake leads to post prandial inflammation and oxidative stress (18-22). Inflammatory mediators, such as Interleukin-1 and tumor necrosis factor-α have a suppressive effect on the gonadal axis (23). However, the decline in testosterone postprandially seems to occur earlier than the induction of inflammation. In one study, the decline in testosterone preceded the rise in interleukin-6 and 17 by over an hour (10). Many meal studies also show that inflammation and oxidative stress are mostly seen after two hours of meal ingestion. Furthermore, meal induced

inflammation varies according to the type of macronutrient (24). In contrast, the decline in testosterone is largely similar, regardless of the type of macronutrient ingested (1). Thus, it is not likely that inflammation is the driver of post-prandial decline in testosterone.

It has been observed that intravenous glucose or lipid infusion does not lower testosterone (10, 25). The effect is only after oral macronutrient intake. It is possible that the release of incretins following oral food intake may have a role in mediating the postprandial decline in testosterone. While only a handful of studies have investigated this possibility, the results do not seem supportive. In one study, glucagon like peptide (GLP)-1 rise after meal did not correlate with the decline in testosterone (15). Infusion of GLP-1 was found to decrease the number of testosterone pulses and increase the duration of pulses, but it did not change the testosterone concentrations (16). Treatment with GLP-1 agonists also does not lower testosterone (26, 27). It is possible that postprandial decline in testosterone is autonomic/neural mediated. It is not known if this phenomenon is observed in men with altered gut anatomy, such as gastric bypass surgery.

In conclusion, our data show that oral glucose ingestion does not lower testosterone concentrations in men on testosterone therapy. Hypogonadism is common in men, and testosterone therapy is prescribed on a regular basis by endocrinologists, urologists, and primary care providers. Endocrinology societies should consider clarifying in their recommendations that fasting testosterone concentrations are required for diagnosis of hypogonadism, but not for monitoring testosterone therapy.

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Figure 1: Testosterone concentrations following oral glucose ingestion at week 0 (before testosterone therapy, white circles) and week 23 (after testosterone therapy, black circles). *P=0.005 for 60 minutes and 0.02 at 90 minutes, as compared to baseline.

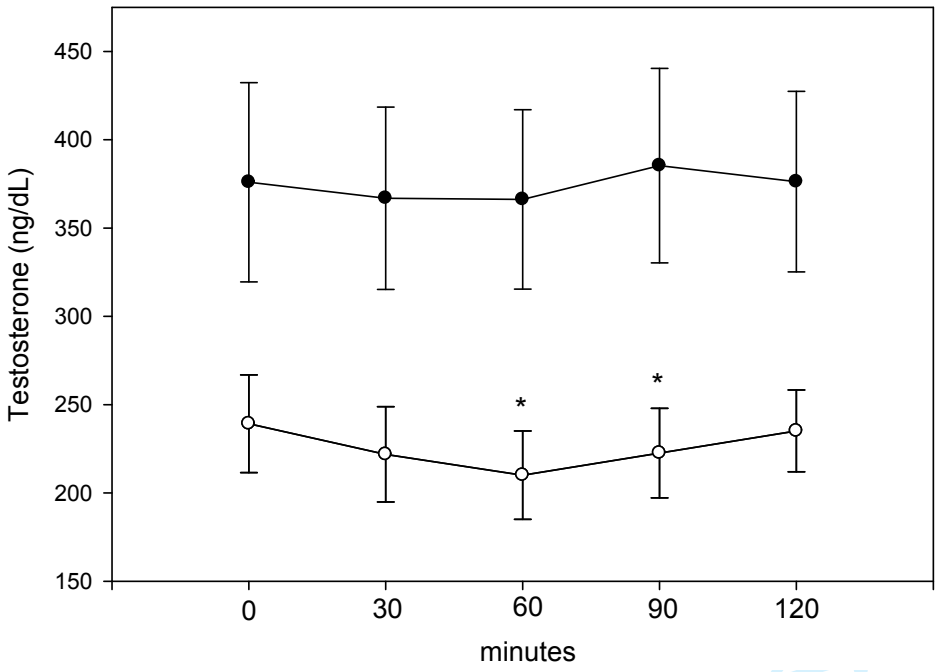
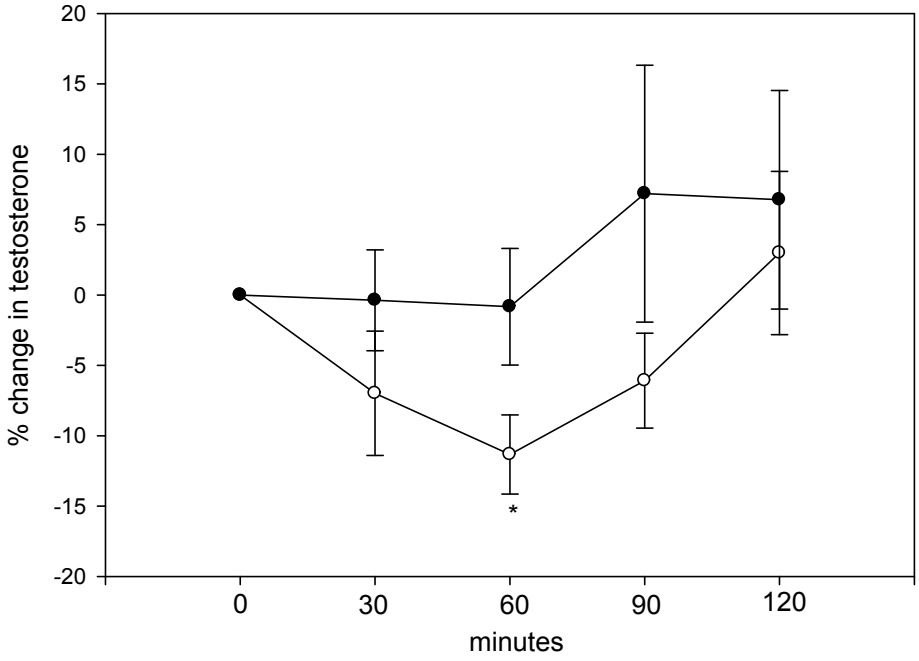


Figure 2: Percentage change in testosterone concentrations following oral glucose ingestion at week 0 (before testosterone therapy, white circles) and week 23 (after testosterone therapy, black circles).

*P=0.002 as compared to baseline



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