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Clomiphene Citrate Effectively Increases Testosterone in Obese, Young, Hypogonadal Men

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Abstract

Background: Obesity has been associated with low testosterone (T) in adult males and in pubertal boys. Therapy for hypogonadism with exogenous T may lead to testicular atrophy and later infertility. Only a few studies have demonstrated that the Selective Estrogen Receptor Modulator (SERM) clomiphene citrate (CC), an estrogen receptor antagonist, increases T in obese hypogonadal men while preventing testicular atrophy. No studies to date using CC have been done in younger obese post-pubertal hypogonadal males.

Objective: To determine whether CC therapy is effective in increasing serum T levels in hypogonadal post-pubertal obese males 18-21 years.

Materials and Methods: A retrospective chart analysis of records in obese men aged 18-21 years was done. Patients with early morning T level <350 ng/dl were given 25 mg CC on alternate days. Out of 18 patients found to have low T, 11 were analyzed. Baseline serum T, LH, FSH, weight and BMI were compared at baseline and after 3 months of CC treatment.

Results: Baseline T level was 233 ± 66 ng/dl and increased to 581 ± 161 ng/dl (p<0.0001) after 3 months of CC treatment. Baseline LH levels increased from 3.3 ± 1.6 mIU/mL to 5.7 ± 1.7 mIU/mL (p=0.027). Similarly, baseline FSH levels increased from 2.8 ± 1.5 mIU/mL to 6.2 ± 3 mIU/mL after CC treatment (p=0.026). There was no correlation between baseline or post treatment weight or BMI and the T level, LH, or FSH level.

Conclusion: This is the first study reporting on CC therapy in obese, hypogonadal post-pubertal men 18-21 years. The SERM CC increased T in obese post-pubertal hypogonadal men, similar to efficacy of CC in adult hypogonadal men over the age 21 years. Larger randomized controlled studies to study the safety and potential use of CC to improve T in young obese HG men are needed.

Keywords: Testosterone; Hypogonadism; Obesity; Men; Young; Clomiphene

Background

Obese boys enter puberty later than leaner boys, and have significantly lower testosterone (T) levels compared to leaner boys of the same Tanner stage [1,2]. This finding is similar to obese adult men who have lower T than leaner men [3,4]. By the age of 18-21 years most young adults achieve an adult morning T level >350 ng/dl, and any T level below 350 ng/dl is considered in the hypogonadal range [3,4]. Low T is associated with development of diabetes [5,6] and independently associated with nonalcoholic fatty liver disease (NAFLD) [7], dyslipidemia and insulin resistance [4]. Suboptimal T is also associated with poor muscle mass, progressive weight gain, fatigue, osteoporosis, gynecomastia, depression, anemia and progression to metabolic syndrome (MS) [3-7].

Hypogonadism (HG), defined as a low serum T accompanied with a constellation of symptoms, such as fatigue, loss of libido, poor exercise tolerance along with reduced fertility (low sperm counts), is of growing concern to clinicians, as the prevalence of HG in the US has increased over time [8]. Two forms of HG have been identified: primary and secondary. Primary HG is the result of gonadal dysfunction. Primary HG can be treated only with exogenous replacement with T [9].

Secondary HG is caused by dysfunction of the central component of the hypothalamic-pituitary-gonadal (HPG) axis [8]. With an increasing prevalence in the United States, obesity appears to be the leading cause of secondary HG and obesity-associated hypogonadism is more common than all other causes combined [9-11]. Other causes of secondary HG and/or reduced fertility in males include drug exposures and/or drug abuse involving the following: marijuana, cocaine, methamphetamines, and opioid narcotics, and anabolic-androgenic steroids. All of these agents can negatively impact male fertility, and adverse effects have been reported on the hypothalamic-pituitary-testicular (HPT) axis, sperm function, and testicular structure. Also, HIV and AIDS, diabetes, hemosiderosis, uremia and other less common genetic and acquired causes can contribute to both primary and secondary HG [9].

Secondary HG can be treated not only through exogenous T replacement but also through stimulation of HPG-axis to increase

gonadotropin release. Direct T administration inhibits central gonadotropin release by a negative feed-back on the HPG axis. This reduces secretion of LH and FSH. Patients receiving direct T replacement therapy are at-risk for testicular atrophy and azoospermia, consequences that are particularly detrimental to patients desiring fertility [12,13]. This adverse effect of exogenous T administration can be avoided by utilizing non-T-based strategies, such as Clomiphene citrate (CC) or Human Chorionic Gonadotropin (hCG) [14]. CC is a Selective Estrogen Receptor Modulator (SERM) and acts as a weak antagonist of estrogen at the level of the hypothalamus, enabling inhibition of central estrogen feedback. This estrogen blockade results in increased GnRH production. GnRH acts on the pituitary gland to increase LH and FSH, which exert their effects on the testicle by increasing Leydig cell T synthesis and Sertoli cell spermatogenesis, respectively. Therefore, CC has been utilized in patients with central HPG-axis dysfunction. [15]. Although, hCG has been successfully used to raise T levels, it is more costly than CC and more difficult to administer [14]. CC is a well-studied SERM. Studies done using CC in older hypogonadal men (age >21 years) show increases of T>550 ng/dL [16,17]. CC doses of 25 mg every other day to 50 mg daily have been used in these studies. Also, a majority of studies have used a total testosterone level of <350 ng/dL to define HG or more appropriately low T levels (in the absence of symptom or fertility data).

Most of the studies done so far have been in hypogonadal men older than 21 years, but do not have HG exclusively due to obesity [15-20]. Also, younger hypogonadal men (<21 years) with obesity, who may be more vulnerable to testicular atrophy with exogenous T, have not been studied.

Subjects and Methods

This study was a retrospective chart review using medical and laboratory records from patients seen at our Pediatric Endocrinology clinic at a Children's Hospital in a rural state between July 2009 and December 2012. Secondary HG was defined as a fasting early morning (8-10 am) serum total T level <350 ng/dl, with a low or normal LH and FSH level. T was measured using liquid chromatography tandem mass spectrometry and equilibrium dialysis. LH and FSH were measured using a chemiluminescent assay. A total of 450 charts of obese or overweight males aged >15 years were reviewed for this study. Inclusion criteria were: overweight (BMI >85 percentile) or obese (BMI >95 percentile) hypogonadal young men 18-21 years old who had been treated with 25 mg CC on alternate days for HG, for at least 3 months. Only charts that had all hormone levels both at baseline and at 3 months were analyzed. Baseline levels (before starting CC) of T, LH and FSH were compared to T, LH and FSH, 3 months after CC therapy. BMI at baseline and at 3 months after CC therapy was compared to levels of T, FSH and LH, before and after CC treatment. Patients with less than 3 months of treatment or poor compliance, defined as missing CC doses more than once a week, were excluded from analysis.

Specifically, subjects with history of hypogonadism, pan-hypopituitarism, severe depression or psychiatric illness, diabetes, head trauma, renal failure, hemochromatosis, cirrhosis, hepatitis C, HIV, treatment with testosterone or oral steroids were excluded. Additionally active infection or recent surgery or hospitalization in the month prior to the baseline tests was exclusion criteria as well.

Of the 450 charts of obese or overweight males analyzed, 18 male subjects were between 18-21 years of age, who met all inclusion criteria. Of these, 11 subjects had pre and post CC T levels but no LH and FSH level was available in 1 subject. A paired t-test was used as a measure of statistical significance to compare hormone levels and BMI at baseline compared to outcome at 3 months (Table 1).

Parameter	N	Baseline	After Treatment	P Value
		Mean (SD)	Mean (SD)	
Total testosterone, ng/dL	11	233 ± 66	581 ± 161	<0.0001
LH, mIU/mL	10	3.3 ± 1.6	5.7 ± 1.7	0.027
FSH, mIU/mL	10	2.8 ± 1.5	6.2 ± 3.0	0.026
BMI kg/m^2	11	35.22 ± 4.8	35.29 ± 4.63	0.725
LH: Luteinizing Hormone, FSH: Follicle Stimulating Hormone, BMI: Body Mass Index. P value of <0.05 was considered statistically significant				

Table 1: Effects of 3 months of CC treatment on T, LH and FSH levels in obese/overweight men aged 18-21 years.

Results

T levels increased significantly in all 11 subjects. LH and FSH levels increased in the 10 patients with LH and FSH levels available at 3 months. An average T level of 581 ng/dL was achieved after 3 months of CC therapy. No major side effects were reported. One patient had premature ejaculation and a mild self-limiting rash was seen in another. 3 out of 10 patients developed facial acne with 1 having a moderate-severe form. Most males had an increase in body hair on physical exam. Three patients reported an increased tendency toward irritability or anger which they felt was associated with taking CC. No correlation was observed between BMI at baseline and baseline T, FSH or LH levels. There was no correlation found between BMI at baseline and T, LH, FSH after CC treatment. Similarly, no statistically significant difference was found between weight and BMI at baseline and after CC treatment. There was no correlation between LH or T increase to pre-treatment body weight or BMI (Table 1).

Discussion

Our current study shows a consistent and statistically significant effect of CC in increasing testosterone levels in obese HG young men aged 18-21 years using a very low dose of 25 mg CC every other day. Although no reduction in BMI was found after normalization of T

levels, perhaps due to the short duration of CC therapy (3 mo) and a short observation period.

Increasing prevalence of obesity and diabetes in the US over the last few years now means that obesity may be the leading causes of secondary HG in young obese males [3,10,18]. HG leading to obesity in a vicious cycle poses an important challenge in this vulnerable population who may desire normal fertility.

CC, a SERM, has been of increasing interest to practitioners managing secondary HG. Several studies have evaluated the efficacy and safety of CC therapy in this population mainly as short-term therapy, with most showing improvements in T levels and symptoms of HG. These studies have also demonstrated that CC can effectively increase both gonadotropins and T [15-17,19,20]. This increase in gonadotropins not only improves T levels but may help maintain fertility.

Shabsigh et al. [21] examined 36 patients (average age 39 years) treated with 25 mg CC daily for 4-6 weeks. The T levels rose from a baseline 248 ng/dL to 610 ng/dL, which is similar to the rise seen in our patients. They also found that the T: estrogen ratio improved by about 60%, indicating that there is a disproportionately favorable androgen response with CC. No side-effects were reported. Similarly Tenover et al. compared 8 weeks of CC therapy, in younger (22-35 years) and older (65-84 years) males, measuring pre- and post-treatment T and LH pulsatility. The authors reported a substantially weaker response to CC in the older aged patients (a 32% response in total T vs. 100% response in the younger cohort) [22]. Both of the above studies were short term, and obese males and males younger than 21 years of age were not studied.

The trial with CC done by Moskovic et al. was over 3 years, and CC was tolerated very well by most males with no major side effects [19]. Thus CC seems a relatively safe drug in the short term. We did not see any major changes in BMI in 3 months of CC treatment, which may be due to the short duration of the study, providing very little time for measurable benefits in weight reduction. Also an expected increase in lean muscle mass may have offset any reduction in visceral fat that CC may cause through increased T levels. Also, we were unable to collect meaningful metabolic, bone or behavioral data that may answer questions about the potential use of CC in obese young males with HG, in combination with intensive dietary and exercise counseling. As has been recently seen, obesity-related hypogonadism may start very early in puberty leading to a vicious cycle of progressive obesity and hypogonadism [18]. To answer these questions, better-controlled, longer studies with an emphasis on safety and efficacy in achieving metabolic health need to be done. Also, the decision whether treatment of HG using a SERM such as CC in these young obese males should be considered early may need, longer, better-controlled randomized clinical trials.

There are a few studies and unpublished reports looking at potential use of CC to improve T levels and its effect on sperm. The longest study was done by Katz et al. where they studied 86 men from the years 2002-2006, with T<300 ng/dL, who were given CC every other day. Dose of CC was increased monthly from an initial dose of 25 mg every other day to 50 mg every other day, until a T level of 500-600 ng/dL was reached. Indications were infertility (64%) with other symptoms, including hypogonadal symptoms. Labs (T/gonadotropins) were followed every 6 months; along with Quality of Life (QOL) using the androgen deficiency in the aging male (ADAM) questionnaire tool. This is a 10-question validated questionnaire focusing on key clinical

features of HG. Mean follow-up was for 19 months (range 5-33 months); with a mean age of 29 years, and youngest patient being 21 years old. All men responded hormonally. No tolerance to CC developed. No major side effects with CC use was seen. Obesity as a factor for HG was not measured and patients younger than 21 years were not studied [16].

In another study from 2002-2006 by Moskovic et al., 46 men with T<300 ng/dL treated with 25 mg CC every other day, were studied. The dose of CC was titrated to achieve a T of 500-600 ng/dL similar to the study above. Patient's labs were followed every 6 months (T/gonadotropins). Here the mean age of the men was 44 yrs. The youngest patient was 26 years old. Mean baseline T was 228 ng/dL. Majority of them were treated for infertility. Mean T at 1 year was 612 ng/dL. Mean T at 2 years was 562 ng/dL. Mean T at 3 years was 582 ng/dL. Again obesity as a contributing factor was not addressed [19].

Men treated with CC seldom report any problems, similar to the subjects in our study. CC has been associated with azoospermia in 3 oligospermic old men [23], while a few other unpublished and published studies similar to the one above show improvement in sperm parameters. Possible side effects reported in women include hot flashes, nausea, dizziness, headaches and temporarily blurred vision. Thromboembolism is the most serious potential side-effect of CC, but the untreated state of obesity in itself greatly raises the risk of thromboembolism. Such side effects usually only appear in females however, as they feel the effects of estrogen manipulation much more readily than men [15,24].

Some limitations of our retrospective chart review are that behavioral and sexual symptoms of obesity-related HG using the ADAM questionnaire were not measured, and that data was not collected in a systematic way. Similarly, metabolic parameters and semen studies were not done in this sample.

In conclusion, our study shows that CC is associated with a significant increase in FSH, LH and T levels in obese hypogonadal young men. Well-controlled prospective studies with a longer duration and follow up to determine the safety and efficacy of CC as an effective therapy in HG young obese men are anticipated.

Acknowledgement

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