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Testosterone, Obesity and Insulin Resistance in Young Males: Evidence for an Association between Gonadal Dysfunction and Insulin Resistance during Puberty

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Abstract

Objective—To assess the relationships among obesity, insulin sensitivity, and testosterone in pubertal boys.

Participants—This study included 20 lean, obese, and type 2 diabetic (T2DM) males, the majority of whom underwent a hyperinsulinemic-euglycemic clamp (n=16).

Methods—Glucose disposal (M value), serum testosterone, and body mass index (BMI) z-score were measured. Differences in testosterone were evaluated by group (lean vs. obese vs. T2DM), while regression was performed to evaluate the relationships among testosterone, obesity and insulin sensitivity.

Results—Controlling for Tanner stage, testosterone concentration was significantly lower in obese (p=0.02) and T2DM males (p=0.001) compared to lean males. Furthermore, M value was significantly associated with serum testosterone, even after controlling for BMI and Tanner stage.

Conclusions—These data suggest that obese adolescent boys have lower serum testosterone than controls of the same Tanner stage, and echo the data in adult males associating obesity and insulin resistance with hypogonadism.

Keywords

insulin resistance; insulin sensitivity; obesity; hypogonadism; puberty; type 2 diabetes mellitus

INTRODUCTION

The observation that pubertal onset is occurring at younger ages in females in the past several decades was reported as early as 1997[1], and has received considerable attention in both the scientific literature and the lay press. A recent panel concluded that there is sufficient evidence to suggest that breast development is starting at an earlier age when data from recent cohort studies, such as Pediatric Research in Office Settings Network (PROS), Blood Institute's National Growth and Health Survey, the National Health and Nutrition

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Examination Surveys (NHANES) and the Bogalusa Heart Study, are compared with older studies of pubertal development[2]. Furthermore, the earlier age of pubertal onset appears to coincide with the increasing prevalence of obesity[3]. Girls from the NHANES cohort who matured earlier had a greater body mass index (BMI) than late-onset girls[4]. The PROS study, which was specifically designed to assess pubertal timing in females, similarly found a correlation between breast Tanner stage and BMI z-score in a given age group[1].

In contrast, one small Italian study reported delayed genital development in obese males[5], a pattern opposite to that reported in females. Similarly, analysis of the NHANES cohort suggests that timing of pubertal onset in males is positively correlated with BMI, i.e. leaner males start puberty earlier[4]. A German study found that lean males reached Tanner stage 5 pubic hair at a younger age than obese males, and had higher testosterone concentrations, although no differences in testicular volume were detected[6]. Results of a recent longitudinal study in the US of 401 boys also suggest that obese males start puberty later than lean males[7]. However, other results are conflicting[8], and mechanistic studies are lacking. Therefore, effects of obesity on gonadal development in males remain unclear.

Studies in adult males support a relationship between obesity and decreased total testosterone, sex hormone binding globulin (SHBG), and free testosterone, potentially due to gonadotropin secretory defects[9–11]. The relationship between obesity and hypogonadism appears to be stronger in adult males with insulin resistance, T2DM, and other components of the metabolic syndrome, rather than isolated obesity[12,13]. To our knowledge, the relationship between insulin resistance and gonadal function has not been assessed in obese adolescent males.

Thus, while multiple longitudinal and cross-sectional studies have confirmed the relationship between BMI and pubertal onset in girls[14–17], data regarding the effect of obesity on pubertal timing in males, and the relationship between testosterone and insulin resistance in pubertal males, are limited. The objective of this study was to compare gonadal function during pubertal development, as assessed by serum testosterone concentration, in lean males and in obese males with and without T2DM. Furthermore, we aimed to assess the relationship between testosterone and insulin sensitivity in this cohort.

METHODS

Subjects

A total of 20 pubertal males between the ages of 12 and 19 years were recruited for a study of obesity and insulin resistance in youth. Height and weight were measured for determination of BMI. BMI z-score was calculated using BMI and age. Subjects were classified by BMI percentile as lean (≤85th percentile) or obese (>95th percentile). This group has been previously described in detail[18]. This cohort includes lean, obese, and T2DM adolescents. Obese subjects were matched for BMI with T2DM subjects. Mean age was 15 ± 2 years and Tanner stage was 4.1 ± 0.8 (range 3–5). Pubertal development was assessed by a single pediatric endocrinologist using the criteria established by Tanner and Marshall for pubic hair and genital development. In addition, testicular volume was measured using an orchidometer by a single pediatric endocrinologist and volumes were assigned an equivalent

Tanner stage as follows: Tanner 2 = 3–5 ml vol., Tanner 3 =6–8 ml , Tanner 4 =10–12 ml , Tanner 5 =>12 ml. There was no significant difference in Tanner stage across the 3 groups as assessed by pubic hair and Tanner stage equivalent of testicular volume. A subset of these subjects (n=16) also had insulin sensitivity assessed by hyperinsulinemic euglycemic clamp.

Laboratory measures

Insulin sensitivity was calculated from a 3-hour hyperinsulinemic euglycemic clamp (80 $mU*m^{-2}*min^{-1}$ insulin) following 3 days of limited physical activity and a 3-day fixed-macro-nutrient, weight-maintenance diet, using the glucose disposal rate (M)[19] as previously described[18].

Testosterone was measured on a morning fasting sample, drawn prior to the insulin clamp, by chemiluminescence using the Beckman-Coulter Immunoassay Access System (intra- and inter-assay coefficients of variation (CV) are 2.1% and 5.1%, respectively). Serum glucose was measured using a Cobas Mira Plus Chemistry Analyzer with intra- and inter-assay CV of 0.66 – 1.24% and 3.9 – 4.6%, respectively. Serum insulin was measured by competitive radio-immunoassay (Diagnostic Systems Laboratories, Inc; DSL-1600) with intra- and inter-assay CV of 5.2 and 9.8%, respectively.

Statistical analysis

All analyses assume a two-sided test of hypothesis with an overall significance level of 0.05 (unless otherwise noted) and were performed in SAS v9.2 (SAS Institute Inc., Cary, NC). Kruskal-Wallis and Fisher's exact tests were used to compare characteristics across groups. Pubic hair Tanner stage was used for all subjects in these analyses. ANCOVA regression was used to model testosterone as a function of the following set of variables: group (lean, obese and T2DM) and Tanner stage. Linear regression was used to model testosterone as a function of the following set of variables: Tanner stage, BMI z-score, and M value.

The study was approved by the Colorado Multiple Institution review board, and appropriate consent and assent were obtained.

RESULTS

Subject characteristics

From the total sample of 20 subjects, 7 (35%) were classified as lean, 6 (30%) as obese without diabetes and 7 (35%) as obese with T2DM (Table 1). As expected, BMI z-score was significantly lower in lean subjects (−0.03 ± 0.7, BMI=19.8 ± 0.8 mg/m^2) compared to obese (2.0± 0.43, BMI=30.4 ± 2.3 mg/m^2) or T2DM (2.3 ± 0.41, BMI=32.9 ± 2.7 mg/m^2) subjects, but obese and T2DM subjects had a similar BMI z-score by design.

Obesity and serum testosterone concentration

Serum testosterone concentration was significantly different in the overall comparison across groups (p=0.004) and post-hoc tests revealed significant differences between both the lean and obese (p=0.02) and the lean and T2DM (p=0.001) subjects when controlling for Tanner stage (Figure 1).

Testosterone and insulin sensitivity

In order to further assess whether insulin sensitivity is an independent predictor of serum testosterone concentration, a regression analysis was performed modeling testosterone as a function of M value, BMI z-score and Tanner stage. In these subjects, M value was significantly associated with serum testosterone after controlling for BMI z-score and Tanner stage (p=0.006). For each unit (mmol* kg^{-1} *min^{-1}) decrease in M value, testosterone decreased by 176 nmol/l [28 ng/dL decrease in testosterone for each unit (mg*kg^{-1} *min^{-1}) decrease in M value (95% CI (9.7, 46.3 ng/dl)] (Figure 2).

DISCUSSION

Our results suggest that serum testosterone, after adjusting for Tanner stage, is lower in obese boys with and without T2DM than in lean boys. These data are consistent with reports of lower testosterone concentrations in obese adults.

Furthermore, while BMI contributes to lower serum testosterone concentration in pubertal males, these data suggest that the relative hypogonadism in obese males is related to the degree of insulin resistance. To our knowledge, we are the first to report these relationships among insulin resistance, obesity, and serum testosterone in pubertal adolescent males.

The paucity of recent data regarding pubertal development in males in general and, more specifically, about the effects of obesity on male pubertal development is surprising, especially given the considerable recent attention that these topics have received in females. Two small studies, performed in European populations, suggest that obese boys may have delayed pubertal development. One of these studies also reported lower testosterone concentrations in obese boys[5,6]. Data from NHANES suggest that pubertal development in obese males is not advanced, and may even be delayed[4].

Two more recent studies specifically address effects of obesity on age at onset of pubertal development, and have conflicting results. A large Danish study compared a cross-sectional cohort of boys from 2006 with one from 1991[8]. They found that age of onset of Tanner 2 pubic hair and genital development was negatively correlated with BMI. They also report that age-adjusted testosterone is positively correlated with BMI in the 2006 cohort. Our study does not include males in Tanner 2 puberty. However, it is possible that puberty starts on time in obese males, but that pubertal progression is slower. This possibility is not addressed in the Danish paper. Furthermore, our study includes a more diverse, insulin resistant population. Both our study and the Danish study are cross-sectional, making it difficult to truly assess onset of pubertal development. However, a recent longitudinal study done in the US and specifically designed to assess the relationship between BMI and the onset of pubertal development[7], found that boys in the highest BMI trajectory were more likely to be prepubertal at a given age than their lean counterparts. Our results support the argument that BMI influences testosterone and pubertal development in males. Further longitudinal studies in a larger cohort of young males are needed to explore these relationships.

The association of decreasing serum testosterone concentration with decreasing insulin sensitivity, as measured in these subjects by the gold standard hyperinsulinemic euglycemic clamp, suggests that the relationship between poor gonadal function and insulin resistance described in older adult males is present as early as adolescence. The possibility that insulin resistance may be a significant contributor to hypogonadism in young obese males is a novel finding in this study.

The etiology of this relative hypogonadism in obese pubertal males remains unclear. Leptin concentrations increase early in puberty in both males and females. However, in males, unlike in females, leptin normally declines as puberty progresses[20,21]. It has been postulated that the paradoxically persistently elevated leptin reported in obese males may be responsible for suppression of gonadal function[22]. Alternatively, increased aromatase activity in excessive adipose tissue may cause increased conversion of testosterone to estrogen, increased ratio of estrogens to androgens, and resulting suppression of gonadotropins. However, neither of these explanations takes into account our demonstration of the apparent relationship between insulin resistance and serum testosterone concentration. It is certainly plausible that, as in females, insulin resistance and resulting hyperinsulinemia result in direct gonadal dysfunction in males. However, while insulin resistance-associated gonadal dysfunction in females leads to excess androgen production, in males it may lead to decreased testosterone production.

There are several limitations to our study design. First, this is a small study which lacks longitudinal follow-up of individual subjects. Future studies following obese males during pubertal development are planned to provide such longitudinal information. An additional limitation is that only total testosterone was measured. Reductions in SHBG, previously reported in obese boys[6], could at least partially explain the reductions in total testosterone. Despite a similar relationship between insulin resistance/obesity and SHBG, adult male studies importantly still show a reduction in free testosterone, arguing that decreased total testosterone levels in obese males are not solely an artifact of decreased SHBG. Furthermore, a recent study suggests that lower SHBG is an independent risk factor for progression to T2DM[23].

Despite these limitations, our finding that BMI contributes to hypogonadism in obese males supports and extends the limited data that have been previously published. More importantly, our finding that insulin resistance may be an important contributor to this relationship is unique, and warrants further investigation. These findings are very different from those reported in obese females, who appear to be precocious in sexual development. However, similar to obese females with polycystic ovarian syndrome, the obese boys in the cohort have evidence of dysfunction of gonadal steroid synthesis associated with insulin resistance. These results address a poorly studied area and clearly demonstrate that a more rigorous longitudinal assessment of pubertal progression, gonadal function and insulin resistance in males is necessary.

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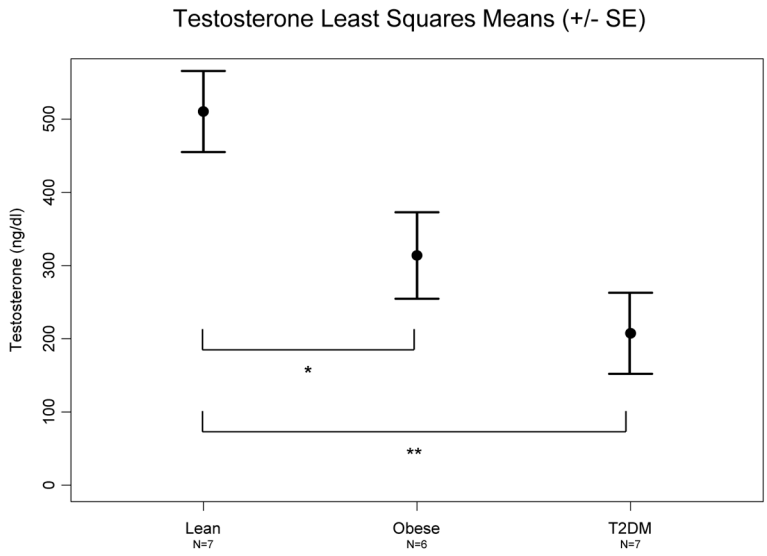

Fig. 1.

Comparison of estimated testosterone between lean, obese and T2DM males. Testosterone concentrations are adjusted for Tanner stage. *Lean vs. Obese p=0.02, **Lean vs. T2DM p=0.001.

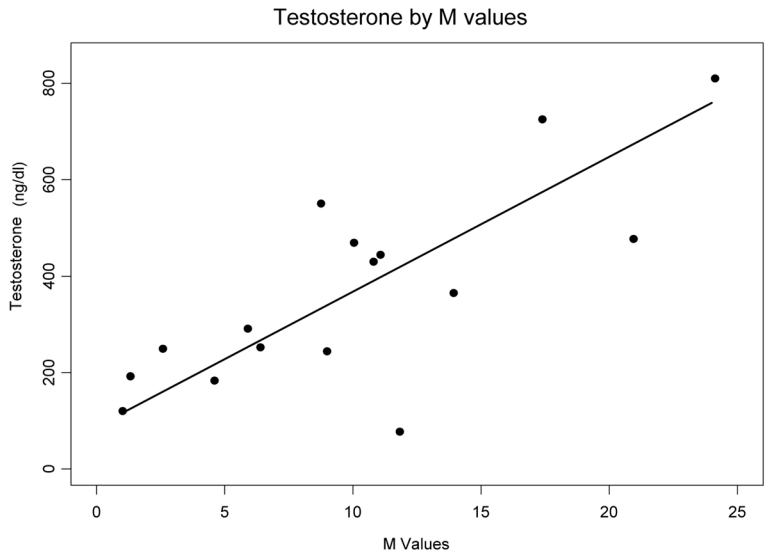

Fig. 2.

Regression analysis of testosterone by M value, controlling for BMI and Tanner stage. p=0.006 (to convert values for testosterone to SI units (nmol/l), multiply by 0.037)

TABLE 1

Subject Characteristics

Characteristic	All (n=20)		Lean (n=7)		Obese (n=6)		T2DM (n=7)		p-value*
	Mean (sd)	Median (range)	Mean (sd)	Median (range)	Mean (sd)	Median (range)	Mean (sd)	Median (range)	
Age	14.9 (2.0)	14.5 (12, 19)	15.7 (1.7)	15.0 (14, 18)	14.5 (2.6)	13.5 (12, 19)	14.3 (1.8)	14.0 (12, 17)	0.31
BMI z-score	0.69 (1.3)	0.81 (−2.6, 2.8)	−0.03 (0.70)	−0.11 (−0.79, 0.96)	2.0 (0.43)	1.9 (1.5, 2.7)	2.3 (0.41)	2.4 (1.7, 2.8)	< 0.0001
Race/Ethnicity**									
White	8 (40%)		5 (71%)		2 (33%)		1 (14%)		0.15†
Hispanic	8 (40%)		1 (14%)		2 (33%)		5 (71%)		
Other	4 (20%)		1 (14%)		2 (33%)		1 (14%)		
Tanner Stage**									
3	3 (15%)		1 (14%)		1 (17%)		1 (14%)		1.0†
4	9 (45%)		3 (43%)		3 (50%)		3 (43%)		
5	8 (40%)		3 (43%)		2 (33%)		3 (43%)		

*Kruskal-Wallis Test

**N (%)

†Fisher's Exact Test

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