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Long-term follow-up of gonadal dysfunction in morbidly obese adolescent boys after bariatric surgery

Vivian L. Chin^{a,b},

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Kristen M. Williams^a,

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Tegan Donnelley,

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Marisa Censani^c,

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Rushika Conroy^d,

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Shulamit Lerner^e,

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Sharon E. Oberfield,

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Ilene Fennoy^{*},

Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, New York, NY, USA.

Donald J. McMahon, and

^{*}**Corresponding author: Ilene Fennoy, MD, MPH**, Department of Pediatrics, Division of Pediatric Endocrinology, Columbia University Medical Center, 622 West 168th Street, PH 17W-307, New York, NY 10032, USA, Phone: (+212) 305-6559, Fax: (+212) 305-4778, if1@cumc.columbia.edu.

^aVivian L. Chin and Kristen M. Williams contributed equally.

^bPresent affiliation: SUNY Downstate Medical Center, Brooklyn, NY, USA.

^cPresent affiliation: Weill Cornell University Medical Center, NY, USA.

^dPresent affiliation: Baystate Medical Center, Springfield, MA, USA.

^ePresent affiliation: Healthy Horizons Pediatric Endocrinology, Riverdale, NY, USA.

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Department of Medicine, Columbia University Medical Center, New York, NY, USA

Jeffrey Zitsman

Department of Surgery, Columbia University Medical Center, New York, NY, USA

Abstract

Background: Elevated body mass index (BMI) is associated with hypogonadism in men but this is not well described in adolescents. The aim is to evaluate gonadal dysfunction and the effects of weight loss after gastric banding in obese adolescent boys.

Methods: Thirty-seven of 54 boys (age 16.2 ± 1.2 years, mean BMI 48.2 kg/m^2) enrolled at the Center for Adolescent Bariatric Surgery at Columbia University Medical Center had low total testosterone for Tanner 5 $<350 \text{ ng/dL}$. Sixteen had long-term hormonal data for analysis at baseline (T0), 1 year (T1) and 2 years (T2) post-surgery. T-tests, chi-squared (χ^2) tests, correlation and linear mixed models were performed.

Results: At T0, the hypogonadal group had higher systolic blood pressure (SBP) (75th vs. 57th percentile, $p = 0.02$), fasting insulin (19 vs. $9 \text{ } \mu\text{IU/mL}$, $p = 0.0008$) and homeostatic index of insulin resistance (HOMA-IR) (4.2 vs. 1.9, $p = 0.009$) compared to control group. Total testosterone was negatively correlated with fasting insulin and HOMA-IR. In the long-term analysis, BMI, weight, waist circumference (WC), and % excess weight decreased at T1 and T2 compared to T0. Mean total testosterone at T0, T1 and T2 were 268, 304 and 368 ng/dL, respectively ($p = 0.07$). There was a statistically significant negative correlation between BMI and testosterone after 2 years ($r = -0.81$, $p = 0.003$).

Conclusions: Low testosterone levels but unaltered gonadotropins are common in this group and associated with insulin resistance. While a significant increase in testosterone was not found over time, the negative relationship between BMI and testosterone persisted, suggesting there may be an optimal threshold for testosterone production with respect to BMI. Long-term studies are needed.

Keywords

bariatric surgery; boys; gastric banding; gonadal function; low testosterone levels; metabolic syndrome; morbid obesity

Introduction

While the relationship between obesity and hypogonadism is well described in adult obese men with and without type 2 diabetes [1–7], much less is known in children. According to the Centers for Disease Control and Prevention (CDC), 14% of boys in the United States were obese in 2000 while 18.6% were affected in 2010 [8]. Despite the increasing prevalence of obesity in boys, little is known about gonadal function in obese adolescents. Few studies report low testosterone levels in this group compared to lean controls [9–13], but this association also differed by pubertal staging. Compared to their lean counterparts, prepubertal obese boys had normal [14] or elevated total testosterone levels [10, 15] while pubertal obese boys had low or normal testosterone levels [10]. Even less is known about gonadal function in adolescent males with extreme obesity, classified as Class II obesity

(body mass index [BMI] ≥ 35 kg/m² or BMI $\geq 120\%$ of the 95th percentile values). We aim to describe gonadal function and associated metabolic abnormalities at baseline in a group of extremely obese adolescent boys and over a 2-year period after metabolic and bariatric surgery (or “bariatric surgery”).

Materials and methods

The study was approved by the Institutional Review Board at Columbia University Medical Center. Written informed consent was obtained from all participants and their parents or legal guardians prior to enrollment. Bariatric surgery using gastric banding is a restrictive type of weight loss surgery that involves placing an adjustable saline-inflatable band around the proximal stomach to create a smaller stomach pouch. All adolescent boys who were evaluated for bariatric surgery at the Center for Adolescent Bariatric Surgery at Columbia University Medical Center had the following pre-surgical and follow-up measures taken: height, weight, waist circumference (WC), systolic and diastolic blood pressure (SBP and DBP), Tanner stage and testicular volume (determined by single endocrinologist by examination using a Prader orchidometer); blood for serum chemistries, reproductive hormones, carbohydrate and lipid markers was obtained and inquiry about drug use was made. Height, weight, WC and BP were measured as previously reported [16, 17]. Laboratory values were performed between the hours of 8:00 am and 10:00 am after an overnight fast with hormonal assays performed at Esoterix, Inc, a specialized clinical endocrine laboratory that measures insulin by immunochemiluminometric assay, total testosterone by liquid chromatography/tandem mass spectrometry (LC/MS-MS) and luteinizing hormone (LH) and follicle stimulating hormone (FSH) by electrochemiluminometric assay. Glucose, lipids, liver function tests and chemistries were performed at the in-house clinical laboratory of New York Presbyterian Hospital. The homeostatic index of insulin resistance or HOMA-IR was calculated using the following formula [18]:

$$\text{HOMA-IR} = \frac{\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose } (\text{mmol/L})}{22.5}$$

BMI was calculated as weight (kg) divided by height² (m²). Height percentile, weight percentile, BMI percentile and BMI z-score adjusted for age and sex were calculated using Epi Info, version 3.5.3, provided by the CDC. BP percentile adjusted for height and sex was calculated based on the fourth report using an online calculator from Uptodate.com [19]. Percent excess weight is calculated as excess weight over ideal body weight at BMI 85th percentile divided by ideal body weight. Metabolic syndrome (MeS) is defined using the modified Cook criteria if three of the following five were met: (1) fasting blood glucose ≥ 100 mg/dL, modified to the 2003 American Diabetes Association criterion, (2) triglycerides (TG) ≥ 110 mg/dL, (3) high-density lipoprotein (HDL) ≤ 40 mg/dL, (4) WC ≥ 90 th percentile for ethnicity, age and sex and (5) SBP or DBP ≥ 90 th percentile for age, height and sex [20].

Subjects

Fifty-four boys were enrolled in the bariatric program with mean ages 16.3 ± 1.2 years (range 14–18), testicular volume 15–20 mL on exam by a single examiner and BMI 48.2 ± 7.9 kg/m² (range 35–71). Thirty-seven of the 54 boys were classified as hypogonadal by low total testosterone levels (<350 ng/dL) for Tanner 5 males (see Table 1 for baseline characteristics). Subgroup analysis of 16 boys with long-term hormonal data following gastric banding was performed over time from baseline pre-surgery (T0), 1 year post-surgery (T1) and 2 years post-surgery (T2). There were no significant differences in terms of weight loss (BMI and weight change) between the boys with ($n = 16$) and those without long-term hormonal data ($n = 21$) (data not shown).

Statistics

Group comparisons were completed using two-tailed Student's t-test, chi-squared (χ^2) test or Mann-Whitney U test using SAS software. Pearson correlation was performed using Excel. An alpha level of 0.05 or less was considered statistically significant. At baseline, a stepwise logistic regression model was used to predict the likelihood of hypogonadism by age, BMI, SBP percentile, DBP percentile, fasting glucose, fasting insulin, hemoglobin A1c (HgbA1c), HOMA-IR, cholesterol, TG, HDL, low-density lipoprotein (LDL), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and all of their first order interactions (SAS 9.4, Proc Logistic, Cary, NC, USA).

For long-term data analysis, linear mixed models were used for comparisons between T0, T1 and T2, and regression analysis of testosterone and MeS as well as its components (DBP, SBP, HDL, TG, fasting blood sugar) was performed.

Results

Thirty-seven boys in the hypogonadal group had lower mean testosterone of 214 ng/dL, while 17 in the normal testosterone group had mean testosterone of 403 ng/dL ($p < 0.0001$). Normative values reported were FSH 2.6–11 mIU/mL for Tanner 5 and LH 0.4–7 mIU/mL for Tanner 4–5. In the hypogonadal group, 13 subjects had low FSH only (<2.6 mIU/mL) and only one subject had borderline elevated LH only of 11 mIU/mL. In the normal testosterone group, five subjects had low FSH only. Overall, the two groups had similar gonadotropin levels and testicular sizes.

The differences between the hypogonadal group and the normal testosterone group are shown in Table 1. Although similar in BMI and central obesity as measured by WC, the hypogonadal group had higher SBP (75th vs. 57th percentile, $p = 0.02$). While 75th vs. 57th percentile for BMI might not have clinical significance, there were two boys in the control group and four in the low testosterone group who had SBP 95th percentile for age, sex and height (definition of hypertension). Abnormalities in glucose metabolism were evident with greater fasting insulin (19.1 vs. 8.9 μ IU/mL, $p = 0.008$) and HOMA-IR (4.2 vs. 1.9, $p = 0.009$) when compared to the normal testosterone group. The other metabolic parameters measured including lipids and liver function tests were not statistically different between the

two groups. No significant association between testosterone and presence of MeS or individual MeS risk factors (DBP, SBP, HDL, TG, fasting blood sugar) was found.

After entering factors such as age, insulin level, SBP, FSH and HOMA-IR into step-wise logistic regression modeling, the final model of FSH (odds ratio [OR] 1.69) and HOMA-IR (OR 8.15) predicted hypogonadism after adjusting for age. The interaction between FSH and HOMA-IR was protective against low testosterone (OR 0.677).

Whole group correlation was done for testosterone and other factors (Table 2). Testosterone negatively correlated with fasting insulin level and HOMA-IR.

In the subgroup analysis of those with long-term hormonal data ($n = 16$), there was a statistically significant decrease in BMI, weight, WC and percent excess weight at T1 and T2 compared to baseline (Table 3). From baseline, HgbA1c decreased at T1 and T2, while fasting insulin only improved at T1 but not T2. There was no significant change in FSH or LH levels over time or in the number of patients who were classified as hypogonadal ($p = 0.131$). Analysis of mean total testosterone at baseline, 1 year and 2 years revealed only a trend toward increasing testosterone from baseline to 2 years ($p = 0.069$). There was a statistically significant negative correlation between BMI and testosterone after 2 years ($p = 0.003$, $r = -0.811$) (Table 4 and Figure 1). See Figures 2 and 3 for non-significant correlation between BMI and baseline testosterone and testosterone after 1 year, respectively.

Discussion

Sixty-nine percent of the adolescent boys with extreme obesity enrolled in the bariatric surgery program had low total testosterone levels, which is quite significant when only 40% of obese men without diabetes and 25–50% with type 2 diabetes are affected by subnormal free testosterone [2, 3, 6]. We observe that most of these adolescents have gonadotropins that fall in the normal range. Thus, hypogonadism in this study does not appear to be associated with altered gonadotropin levels, in contrast to obesity-associated hypogonadotropic hypogonadism in men [21]. Some have proposed that in obese boys, excess estradiol due to increased adiposity is associated with lower testosterone levels and smaller testicular size during adolescence [22]. However, testicular size was similar between groups in our study despite excessive adiposity. Estradiol levels were not measured as part of this study, but should be investigated in the future. Other proposed mechanisms linking obesity with low testosterone included insulin resistance leading to decreased sex hormone binding globulin (SHBG), severe obesity suppressing FSH and LH [23], elevated estrogen levels inhibiting LH centrally or elevated leptin from adipose tissue or other peptides acting centrally and peripherally to damage Leydig cells [24]. In obese mice, excessive oxidative damage and elevated leptin levels are associated with Leydig cell pathology [25]. While none of the boys had elevated FSH, higher FSH predicted hypogonadism by regression analysis which may indicate some level of subclinical primary gonadal dysfunction. How the interaction between FSH and HOMA-IR protects one from hypogonadism remains to be seen.

In the adolescent population, a few studies have described lower total testosterone levels in obese boys [9, 11, 12, 26], while conflicting studies report similar levels of androgens

between obese pubertal children and their controls [10, 14]. Vandewalle et al. described low total and free testosterone levels in a group of obese adolescent males with mean BMI of 36.2 kg/m² who were in late puberty (Tanner stage 5) compared to age-matched lean controls [26]. To the best of our knowledge, our study is one of the few describing low testosterone levels in the adolescent males with extreme obesity with even higher average BMI of 48.2 kg/m². Mogri et al. found that late-adolescent obese boys had 40–50% lower total, percent free and calculated free testosterone than their lean counterparts after controlling for age and Tanner stage [13]. In their obese group, 12% had low total testosterone (below 161.3 ng/dL), while none were affected in the lean group. Testosterone was negatively correlated with HOMA-IR and BMI, which is similar to our finding. We describe additional negative correlations of testosterone with fasting insulin and SBP percentile. The boys in our study were heavier and more metabolically unhealthy and these factors were associated with lower testosterone levels.

To the best of our knowledge, this study is the first to provide long-term hormonal analysis in a group of adolescent boys with extreme obesity undergoing bariatric surgery. Even though not statistically significant, our study suggests that 1 and 2 years after bariatric surgery, testosterone levels improve from baseline. This change is associated with weight loss, decreased WC, decreased A1c and decreased fasting insulin levels. The association of weight loss and improvement in total testosterone and SHBG has been described in adult men who undergo bariatric surgery [27–30]. We found that a negative relationship between total testosterone and BMI had persisted 2 years after surgery, suggesting that there is a critical BMI threshold at which testosterone is produced. Hoftra et al. had described a similar inverse relationship between total and free testosterone levels, with BMI in obese men [31].

In a study of testicular function, obese adolescent males had lower insulin-like factor 3 (INSL3), a marker of Leydig cell function, which strongly correlates with testicular growth during puberty. Subjects in this study also had lower total testosterone, lower serum LH and higher leptin levels than their lean counterparts, lending support for obesity affecting testicular function in pubertal obese boys [12]. While leptin receptors have been found on Leydig cells [32], leptin and leptin receptor expression have been associated with decreased testosterone levels, implying that leptin could contribute to testicular dysfunction in obesity [12, 33]. On the other hand, testosterone and dihydrotestosterone were both able to reduce leptin secretion by up to 62% in human adipocytes in primary culture [34]. Leptin and markers of Leydig and Sertoli cell function should be investigated further to clarify the pathogenesis of hypogonadism in boys with extreme obesity.

Consistent with obese adolescent males who had a hyperinsulinemic-euglycemia clamp study [9], we also found that low testosterone is associated with insulin resistance as measured by higher insulin levels in the hypogonadal group. In our study, group comparison revealed higher SBP percentile being associated with the hypogonadal group, supporting the concept that low testosterone may be a consequence of metabolic dysfunction in obesity. Further investigation is warranted to clarify the relationship between obesity, gonadal dysfunction, insulin resistance and metabolic abnormalities in the extremely obese adolescent male.

Measurement of total and free testosterone in adolescence has its limitations and considerations. Even though free testosterone or SHBG levels were not obtained, using low total testosterone by LC/MS-MS, a sensitive and specific assay, as a measure of hypogonadism is valid. According to the Endocrine Society Position statement [35], free testosterone has limited value in boys given the lack of normative data in this age group and total testosterone measurements should be carried out with a sufficiently sensitive assay such as LC/MS-MS, which was used in our study. In addition, due to the lack of standardized values, using free testosterone as a measure of hypogonadism would be difficult. Another limitation was that this was a retrospective analysis that only included 54 boys, out of which only a subset of 16 had long-term hormonal data available. Statistical power may not have been achieved due to small numbers but despite this, we found significance in certain parameters in relation to testosterone (BMI, HOMA-IR and fasting insulin were negatively correlated).

The generalizability of our data is limited by the small sample size, representing a convenience sample obtained from a cohort of males enrolled in a single-center bariatric program. As a result, selection bias cannot be ruled out. Furthermore, though the modified Cook criteria were used to define MeS, there is no single definition used for childhood MeS, precluding a clear understanding of the relationship between male gonadal function and the term “metabolic syndrome”. And lastly, our results are based on boys who lost weight as a function of laparoscopic gastric banding. This procedure has fallen out of favor compared to other metabolic and bariatric surgeries, necessitating an analysis of outcomes after these procedures to ensure relationships bear no specific relationship with the procedure performed.

Conclusions

Low total testosterone without any detectable gonadotropin disturbance is prevalent and affected 69% of our group of adolescent males with extreme obesity enrolled in a bariatric surgery program. Hypogonadism is associated with insulin resistance, BMI and elevated SBP. Two years post-surgery, a trend toward increasing testosterone was observed, and the negative relationship between BMI and testosterone persisted, suggesting that there may be an optimal threshold for testosterone production with respect to BMI. Long-term studies are needed to further evaluate the effect on body composition, fertility and overall sense of well-being.

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Figure 1:
Correlation between body mass index and T2 testosterone levels (n = 16).

Figure 2:
Correlation between body mass index and baseline testosterone levels (n = 16).

Figure 3:
Correlation between body mass index and T1 testosterone levels (n = 16).

Table 1:

Clinical characteristics for whole group (n = 54) and between low and normal testosterone groups, expressed as mean (SD).

	Boys eligible for surgery (n = 54)	Low testosterone (n = 37)	Normal testosterone (n = 17)	p-Value ^a
Age, years	16.3 (1.2)	15.8 (1.2)	15.9 (1.2)	0.37
Testicular volume, cm	18.7 (2.2)	19 (2)	19 (2)	0.833
Weight, kg	145.7 (34.4)	322.8 (64)	296.8 (52)	0.12
BMI, kg/m ²	48.2 (7.9)	45.7 (8.7)	44.3 (5.7)	0.54
Waist circumference, cm	137.6 (16.2)	140 (17)	133 (14)	0.162
Systolic BP, mmHg	124 (9)	125 (8.9)	121 (9.2)	0.08
Systolic BP, percentile	69 (25)	75 (22.4)	57 (27.0)	0.02
Diastolic BP, mmHg	79 (8)	79 (8.3)	78 (8.8)	0.68
Diastolic BP, percentile	78 (20)	80 (16.7)	72 (25.5)	0.41
Fasting insulin, μ U/mL	15.9 (14.1)	19.1 (15.4)	8.9 (7.3)	0.0078
Fasting glucose, mg/dL	86 (8.7)	84 (9.3)	80 (7.0)	0.13
HOMA-IR	3 (3.1)	4.2 (3.4)	1.9 (1.7)	0.0093
HgbA1c, %	5.7 (0.4)	5.7 (0.5)	5.5 (0.3)	0.17
LH, mIU/mL	3.5 (1.5)	3.4 (2.2)	3.4 (1.4)	0.98
FSH, mIU/mL	3.5 (2.0)	3.4 (2.0)	3.7 (2.0)	0.53
Total testosterone, ng/dL	273 (114)	213.8 (70.5)	402.5 (75.7)	<0.0001
Cholesterol, mg/dL	165 (33)	164.3 (34.1)	166.4 (33.7)	0.83
HDL, mg/dL	38 (7.5)	37.2 (7.0)	40.9 (8.3)	0.10
LDL, mg/dL	101 (30)	101.1 (33.6)	101.5 (23.1)	0.96
Triglycerides, mg/dL	127 (74.9)	130.0 (73.0)	119.6 (82.8)	0.65
AST, U/L	30 (45.5)	32 (55.4)	25 (8.1)	0.43
ALT, U/L	31 (19.7)	32 (22)	27 (15)	0.85

^aTwo-tailed t-tests or Mann-Whitney U test (for non-parametric test) with significance set at <0.05, between low and normal testosterone groups. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BMI, body mass index; FSH, follicle stimulating hormone; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c; HOMA-IR, homeostatic index of insulin resistance; LDL, low-density lipoprotein; LH, luteinizing hormone; SD, standard deviation. Bold p-values are significant.

Table 2:

Correlation with total testosterone at T0 (r) (n = 54).

	r	p-Value
Age	0.25	0.06
BMI	−0.12	0.37
Testicular size	0.15	0.29
Waist circumference	0.02	0.90
Systolic BP	−0.13	0.36
Diastolic BP	−0.02	0.90
Fasting insulin	−0.38	0.004
Fasting glucose	−0.03	0.80
HgbA1c	−0.21	0.13
HOMA-IR	−0.37	0.007
LH	0.08	0.55
FSH	0.06	0.68

BP, blood pressure; BMI, body mass index; FSH, follicle stimulating hormone; HgbA1c, hemoglobin A1c; HOMA-IR, homeostatic index of insulin resistance; LH, luteinizing hormone. Bold p-values are significant.

Long-term follow-up of hypogonadal males before and after bariatric surgery (n = 16), reported as mean (SD).

Table 3:

	Baseline (T0)	1 year (T1)	2 years (T2)	p-Value
Age, years	16.0 (1.2)			
Weight, kg	138.0 (19.0)	122.3 (20.5)	119.7 (26.3)	<0.0001 ^a
				<0.0001 ^b
				0.7939 ^c
BMI, kg/m ²	46.4 (6.1)	40.4 (6.8)	39.7 (8.6)	<0.0001 ^a
				<0.0001 ^b
				0.9061 ^c
Waist circumference, cm	134.7 (11.9)	126.0 (16.2)	126.8 (19.1)	0.0057 ^a
				0.0079 ^b
				0.9438 ^c
Percent excess weight	91.9 (24.3)	58.5 (25.0)	50.5 (31.9)	<0.0001 ^a
				<0.0001 ^b
				0.1959 ^c
Hemoglobin A1c, %	5.6 (0.5)	5.3 (0.6)	5.0 (0.4)	0.0312 ^a
				0.0017 ^b
				0.3886 ^c
Fasting insulin, mIU/mL	17.2 (14.0)	8.1 (6.7)	10.1 (8.0)	0.0149 ^a
				0.0702 ^b
				0.9197 ^c
FSH, mIU/mL	3.1 (1.8)	3.0 (1.8)	2.6 (1.6)	0.9880 ^a
				0.9271 ^b
				0.8788 ^c

	Baseline (T0)	1 year (T1)	2 years (T2)	p-Value
LH, mIU/mL	3.7 (2.7)	5.1 (2.1)	4.2 (1.6)	0.1243 ^a
				0.2392 ^b
				0.9877 ^c
Testosterone, ng/dL	267.6 (145.4)	303.8 (108.4)	348.4 (91.1)	0.6123 ^a
				0.0697 ^b
				0.3120 ^c

p < 0.05 is significant

^aT0 and T1

^bT0 and T2

^cT1 and T2. BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; SD, standard deviation. Bold p-values are significant.

Correlation coefficients (r) between metabolic syndrome risk factors and testosterone levels (n = 16).

Table 4:

	BMI	Diastolic BP	Systolic BP	HDL	Triglyceride	Fasting blood sugar
Testosterone (T0)	-0.004	0.209	-0.160	-0.177	-0.128	0.295
Testosterone (T1)	-0.171	0.206	0.131	-0.124	0.252	-0.425
Testosterone (T2)	-0.811^a	-0.493	-0.217	0.172	-0.002	0.080

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein. Bold p-values are significant.

^aStatistically significant p < 0.05.