The relationship between the level of serum-free testosterone and depression in obese adolescent men in Sharkia Governorate
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Background
Obesity among children and adolescents is considered as one of the most serious public health concerns; low levels of testosterone have been associated with higher levels of morbidity and may have been associated with depression.

Objective
To assess the relationship between the level of serum-free testosterone and depression in obese adolescent men in Sharkia Governorate.

Patients and methods
The present study was conducted on 240 age-matched healthy Egyptian adolescent men, collected from the obesity clinic, Internal Medicine Department, Zagazig University Hospital and five high schools in Sharkia Governorate; all the included participants were subjected to: (a) history taking; (b) physical examination (weight, height, BMI, waist circumference, waist to hip ratio, and Tanner stage using Prader orchidometer); (c) hormonal investigations (free testosterone, estradiol, follicular-stimulating hormone, and luteinizing hormone); (d) psychological assessment for depression using: Mini International Neuropsychiatric Interview for Children and Adolescents and children’s depression inventory.

Results
There was a significant inverse correlation between free testosterone levels and waist circumference among both control and obese cases ($r=-0.31, P=0.031$ and $r=-0.30, P=0.01$, respectively). The free testosterone level was significantly lower in obese cases with depression (2.81±2.32 pg/ml) in comparison with obese cases without depression (3.63±2.65 pg/ml) ($P=0.04$) and testosterone levels was significantly lower in obese cases having some depressive symptoms (feeling depressed, feeling restless, feeling guilty, eating disorders, sleeping disorders, feeling restless, and suicidality). There were significant inverse correlations ($P<0.05$) between mean free testosterone level and both mild and moderate depression ($r=-0.45, P=0.02$ and $r=-0.58, P=0.012$, respectively), and with the following depressive symptoms; feeling depressed, feeling restless, feeling guilty, eating disorder, sleeping disorders, poor concentration, and suicidality.

Conclusion
Obese adolescent men in Sharkia Governorate are significantly associated with lower free testosterone levels. Most of the depression symptoms and their degree are inversely correlated with the levels of free testosterone, otherwise the levels of luteinizing hormone, follicular-stimulating hormone, and estradiol showed no correlation with the depression symptoms or their degree. We recommend further larger studies to prove the relationship between the level of serum-free testosterone and depression in obese adolescent men and try to put a management protocol.

Keywords:
adolescent men, depression, free testosterone, obese

Introduction
Childhood obesity has more than doubled in children and tripled in adolescents in the past 30 years. In addition to the well-known health risks of obesity, including type 2 diabetes, cardiovascular disease, hypertension, stroke, and certain forms of cancer, obesity is associated with psychiatric illness. Studies of obese individuals show high rates of psychiatric comorbidities, including eating disorders, depression, anxiety, and personality disorders [1].

It has been shown that testosterone concentrations of young obese pubertal and postpubertal men are 40–50% lower than those with normal BMI [2].
Low testosterone levels in men were associated with high incidence of depressive illness and were correlated also with the severity of depression symptoms [3].

Obesity among children, adolescents, and adults has emerged as one of the most serious public health concerns. The worldwide prevalence of childhood obesity has increased strikingly over the past 3 decades [4].

The growing prevalence of childhood obesity has also led to the appearance of obesity-related comorbid disease entities at an early age. Childhood obesity can adversely affect nearly every organ system and often causes serious consequences, including hypertension, dyslipidemia, insulin resistance, dysglycemia, fatty liver disease, and psychosocial complications. Obesity is associated also with a high prevalence (25–33%) of hypogonadotropic hypogonadism in adolescents, middle-aged, and elderly men. Several studies have shown a negative impact of obesity on testosterone levels in adolescents. The possible mechanisms beyond this phenomenon are reduced hypothalamic and pituitary secretory functions, excess estrogen production, and reduced circulating sex-hormone-binding globulin [5].

Low levels of testosterone have been associated with higher levels of morbidity and mortality in a number of studies [6], and have been associated with depression, fatigue, irritability, impaired cognition, and loss of muscle mass and bone mineral density [7].

Depression is a major burden to society affecting 5–13% of the aged population at any one time. It is an often subtle and commonly missed diagnosis [8].

Therefore, the aim of this study is to assess the relationship between the level of serum-free testosterone and depression in obese adolescent men in Sharkia Governorate.

**Patients and methods**

The protocol of this study was approved by the local ethics committee in October 2016. All procedures performed were in accordance with the ethical standards of the Institutional Research Committee and with the Helsinki Declaration and its later amendments. It was a case–control study conducted on 240 age-matched healthy Egyptian adolescent men reaching puberty with tanner stage from two up to four with age from 11 up to 18 years collected from the Obesity Clinic, Internal Medicine Department, Zagazig University Hospital and five high schools in Sharkia Governorate. After being informed on the purpose and procedures of the study informed consent was obtained from the school directors and/or from parents of our cases.

All cases with obesity caused by genetic syndromes, endocrine diseases or are associated with systemic diseases, neurological disorders, or neurodevelopmental delay, with Tanner stage 1 or 5, past history of psychiatric diseases, on psychotropic drugs, or suspected to be taking any drugs were excluded.

All the included participants will be subjected to the following.

**History taking**

Age, sex, order of birth, history of any medical disease, history of drug intake, history and factors contributing to the development of obesity.

**Physical examination including anthropometric method**

1. **Weight.**
2. **Height.**
3. **BMI**: defined as WHO growth reference [9].
4. **Waist circumference**: to measure the waist circumference, the tape was applied horizontally midway between the lowest rib margin and the iliac crest about the level of the umbilicus [9].
5. **Hip circumference**: measurement was taken at the point yielding the maximum circumference over the buttocks, with the tape held in a horizontal plane. Waist and hip circumferences were measured in all individuals with an elastic tape. For these measurements, the patient was in a standing position [9].
6. **Waist/hip ratio** was calculated after that.

Tanner staging was done to all participants according to Tanner [10], using a Prader orchidometer. Men with testicular a volume of between 4 and 8 ml were classified as Tanner stage 2, those with a testicular volume of between 8 and 10 ml were classified as Tanner stage 3, those with a testicular volume of between 10 and 20 ml were classified as Tanner stage 4, and those with a testicular volume of between 20 and 25 ml were classified as Tanner stage 5.

**Hormonal investigations**

All patients and controls will have the following investigations:

Free testosterone (the normal range in adult men is 5–30 pg/ml).
Estradiol (the normal range in adult men is 0.029–0.03 nmol/l).

Follicular-stimulating hormone (FSH) (the normal range in adult men is 2–15 mIU/ml).

Luteinizing hormone (LH) (the normal range in men is 1.5–9.3 mIU/ml).

The quantitative determination was done using electrochemiluminescence using Cobas 8000 (Roche Diagnostics GmbH, D-68298 Mannheim, Germany).

**Psychometric evaluation**

Psychologic assessment for depression using the following.

*Mini International Neuropsychiatric Interview for Children and Adolescents (module A; major depressive episode)*

The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI) KID was designed as a brief structured interview for the major axis I psychiatric disorders and is divided into modules identified by letters, each corresponding to a diagnostic category; in this study we use only module A (major depressive episode). At the beginning of the diagnostic module A, two screening questions corresponding to the main criteria of the disorder are presented in a gray box, additional symptom questions within the disorder section are asked only if the screen questions are positively endorsed. All questions are in binary ‘yes/no’ format [11].

At the end of module A, two diagnostic boxes permit the interviewer to indicate whether the diagnostic criteria are met.

Answers with an arrow above them indicate that one of the criteria necessary for the diagnosis is not met. In this case, the interviewer should go to the end of the module and circle (NO) in all the diagnostic boxes [12].

*Children’s depression inventory*

Children’s depression inventory (CDI) is a 27-item quantifying symptoms such as depressed mood, hedonic capacity, vegetative functions, self-evaluation, and interpersonal behaviors. Each item consists of three statements graded in the order of increasing severity from 0 to 2; children and adolescents select the one that characterized their symptoms best during the past 2 weeks. The item scores are combined into a total depression score, which ranges from 0 to 54. A higher CDI score means a higher depressive state.

The severity of depression among the study patients according to age and sex is as follows: the age range of adolescent men were from 11 to 18 years with scores range 0–14 have no or minimal depression, patients with scores range 15–21 have mild depression, patients with scores range 22–28 have moderate depression and patients with scores of more than 29 have severe depression [13].

**Statistical analysis**

All analyses were performed with statistical package for the social sciences, 20.0 (IBM, Armonk, New York, USA). All results were expressed as mean and SD values for parametric data.

Student’s *t* test was used to compare between two independent group means for parametric data.

χ² test was used to compare two qualitative groups. Fisher’s exact test was used to determine if there are nonrandom associations between two categorical variables.

**Results**

The results of this study are present in the following tables.

Table 1 shows the comparison between control and obese cases regarding age, anthropometric measures, blood pressure, and testicular volume. There was a highly significant increase (*P*<0.001) among obese cases versus control regarding mean±SD of weight (97.56±13.46 vs. 62.87±5.8 kg) (*P*<0.001), BMI (33.78±4.87 vs. 33.7±1.67 kg/m²), waist circumference (105.88±10.05 vs. 77.88±7.98 cm), waist–hip ratio (0.95±0.21 vs. 0.79±0.13), systolic blood pressure (127.44±9.22 vs. 118.22±7.45 mmHg), and diastolic blood pressure (80.22±5.44 vs. 71.57±4.77 mmHg, respectively).

There was a highly significant decrease (*P*<0.001) among obese cases versus controls regarding right testicular volume (12.56±6.0 vs. 18.10±7.14 ml) and left testicular volume (12.7±5.92 vs. 17.2±6.23 ml, respectively).

There was a highly significant decrease (*P*<0.001) among obese cases versus controls regarding right testicular volume (12.56±6.0 vs. 18.10±7.14 ml) and left testicular volume (12.7±5.92 vs. 17.2±6.23 ml, respectively).

Table 2 shows the correlations between the levels of sex hormones and anthropometric measures among control and obese cases. There is a significant inverse correlation between free testosterone levels and waist circumference among both control and obese cases (*r*=-0.31, *P*=0.031 and *r*=-0.30, *P*=0.01, respectively). But there was no significant
correlations regarding other hormones with anthropometric measures.

Table 3 shows the comparison between mean±SD of free testosterone levels for obese cases with or without each depression symptom in the MINI-KID module A. The mean±SD of free testosterone levels was significantly lower in obese cases having the following depressive symptoms: feeling depressed (2.42±1.2 vs. 3.35±2.32) if not present (P=0.036), feeling restless (2.5±1.5 vs. 3.84±1.9) if not present (P<0.001), feeling guilty (2.36±2.4 vs. 3.5±2.2) if not present (P<0.001), eating disorders (increasing or decreasing appetite) (2.56±2.25 vs. 3.7±2.11) if not present (P<0.001), sleeping disorders (2.61±1.5 vs. 2.89±2.4) if not present (P=0.003), and suicidality (2.1±2.7 vs. 3.76±2.87) if not present, while

The mean free testosterone level was insignificantly different in obese cases having or not the following depressive symptoms: feeling tired, poor concentration and loss of interest.

Table 4 shows the comparison between mean±SD of testicular volume and sex hormones for obese cases with or without depression in the MINI-KID module A. The free testosterone level is significantly lower in obese cases with depression (2.81±2.32) in comparison with obese cases without depression (3.63±2.65) (P=0.04). But there was no significant difference between depressed and not depressed obese case regarding estradiol, FSH, LH, or testicular volumes.

Table 5 shows the comparison regarding hormonal profile between each depression degree according to CDI in obese cases. There were no significant differences between obese cases with mild and moderate depression regarding all sex hormones (P>0.05).

Table 6 shows the correlation between hormonal profile and each depressive symptom according to the MINI-KID module A in obese cases; there is highly significant inverse correlations (P<0.001) between mean free testosterone level and the symptom of feeling depressed (r=-0.5), there is significant inverse correlations (P<0.05) between mean free testosterone level and the following depressive symptoms; feeling restless (r=-0.29), feeling guilty (r=-0.45), eating disorder (r=-0.38), sleeping disorders (r=-0.41), poor concentration (r=-0.29), and suicidality (r=-0.37), while there were nonsignificant correlations (P>0.05) between mean free testosterone level with symptoms of feeling tired (r=0.47) and loss of interest (r=0.53).

Table 7 shows the correlation between hormonal profile and each depressive degree according to CDI in obese cases; there are significant inverse correlations between free testosterone levels and both mild and
Table 3  t test for the comparison between mean±SD of free testosterone levels for obese cases with or without each depression symptom in the Mini International Neuropsychiatric Interview for Children and Adolescents-KID module A

| Depression symptoms | Mean±SD for free testosterone | P value |
|---------------------|-------------------------------|---------|
|                      | With symptoms                 | Without symptoms |
| Feeling depressed    | 2.42±1.2                      | 3.35±2.32 | 0.036 |
| Feeling restless     | 2.5±1.5                       | 3.84±1.9 | <0.001 |
| Feeling tired        | 2.83±1.8                      | 2.77±1.95 | NS |
| Feeling guilty       | 2.36±2.4                      | 3.5±2.2 | <0.001 |
| Eating disorders     | 2.56±2.25                     | 3.7±2.11 | <0.001 |
| Sleeping disorders   | 2.61±1.5                      | 2.89±2.4 | 0.003 |
| Poor concentration   | 2.5±2.0                       | 2.45±1.9 | NS |
| Loss of interest     | 2.1±2.7                       | 3.76±2.87 | <0.001 |

FSH, follicular-stimulating hormone; LH, luteinizing hormone.

Table 4  t test for the comparison between mean±SD of testicular volume and sex hormones for obese cases with or without depression in the Mini International Neuropsychiatric Interview for Children and Adolescents module A

|                      | With depression (mean±SD) | Without depression (mean±SD) | P value |
|---------------------|---------------------------|-----------------------------|---------|
| Right testicular volume (ml) | 12.27±4.13                | 13.4±3.80                   | NS      |
| Left testicular volume (ml)   | 11.65±5.3                 | 13.45±4.43                  | NS      |
| Estradiol (nmol/l)          | 0.07±0.01                 | 0.08±0.02                   | NS      |
| FSH (mIU/ml)               | 14.87±7.64                | 15.32±4.88                  | NS      |
| LH (mIU/ml)                | 8.26±5.67                 | 8.14±4.52                   | NS      |
| Free testosterone (pg/ml)  | 2.81±2.32                 | 3.63±2.65                   | 0.04    |

FSH, follicular-stimulating hormone; LH, luteinizing hormone.

Table 6 Correlation between hormonal profile and each depressive symptom according to the Mini International Neuropsychiatric Interview for Children and Adolescents-KID module A in obese cases

| Depression symptoms | Estradiol (nmol/l) | LH (mIU/ml) | FSH (mIU/ml) | Free testosterone (pg/ml) |
|---------------------|-------------------|-------------|--------------|---------------------------|
|                      | r | P    | r | P    | r | P    | r | P |
| Feeling depressed    | 0.02 | NS | -0.02 | NS | 0.01 | NS | -0.5 | <0.001 |
| Feeling restless     | -0.02 | NS | -0.05 | NS | -0.05 | NS | -0.29 | 0.04 |
| Feeling tired        | 0.07 | NS | 0.09 | NS | 0.14 | NS | -0.09 | NS |
| Feeling guilty       | 0.04 | NS | 0.08 | NS | -0.05 | NS | -0.45 | 0.01 |
| Eating disorders     | 0.07 | NS | -0.07 | NS | -0.01 | NS | -0.38 | 0.01 |
| Sleeping disorders   | 0.08 | NS | -0.03 | NS | 0.02 | NS | -0.41 | 0.04 |
| Poor concentration   | 0.01 | NS | -0.02 | NS | -0.07 | NS | -0.29 | 0.02 |
| Loss of interest     | 0.03 | NS | 0.04 | NS | 0.04 | NS | -0.06 | NS |
| Suicidality          | -0.05 | NS | 0.01 | NS | 0.15 | NS | -0.37 | 0.01 |

FSH, follicular-stimulating hormone; LH, luteinizing hormone.

**Discussion**

The results of our study showed that the mean systolic and diastolic blood pressure was significantly (P<0.001) higher in obese than nonobese adolescent men and this can be due to the activation of the renin–angiotensin–aldosterone system in obesity and also physical compression of the sympathetic nervous system overactivity; all of these eventually lead to an increase in systolic and diastolic blood pressures [14–17].

These results are in accordance with another study [18] in Germany performed on 172 children and adolescents (overweight, obese, and control) found that overweight and obese cases had significant higher blood pressure values compared with the controls.

Also in our study we found that there was a significant decreased right and left testicular volume in obese compared with nonobese adolescent men. Moreover, the hormonal profile for obese and nonobese adolescents was studied and showed that nonobese depression (r=-0.45, P=0.02 and r=-0.58, P=0.012, respectively). Otherwise, there were no significant correlations between levels of other sex hormones and each depressive degree.
adolescents had significantly ($P<0.001$) higher mean values of free testosterone level than obese adolescent men.

Obesity is an insulin-resistant state with an interference with insulin signal transduction and neurons [19] leads to an elevated insulin concentration which is thought to be the cause of reduced levels of sex-hormone-binding globulin [20], leading to decreasing testosterone levels. However, it has been assumed that low testosterone concentration in obese males is secondary to enhanced peripheral aromatization of testosterone to estradiol in the adipose tissue [21], but this is not consistent with the results of our study as we found that obese adolescents had lower estradiol levels compared with nonobese controls; therefore, low free testosterone levels are not the consequence of estradiol-dependent suppression of the hypothalamo-hypophyseal-gonadal axis [22] in obese adolescent men in our study, so the low free testosterone levels in obese adolescent men in our study is probably a result of primary dysfunction of the Leydig cells as a consequence of obesity. Leydig cell impairment starts from pubertal Tanner stage 2 and continues at Tanner stage 4 by decreased serum insulin-like factor 3 (INSL3) levels in obese adolescent boys [10]. INSL3 may be used as a Leydig cell-specific marker for onset progression of puberty in boys. A study done by Taneli et al. [10] confirmed this data by increasing concentrations of INSL3, total testosterone, testis volume in association of progressive pubertal development. Recently, serum INSL3 levels have been measured in normal men and men with different testicular pathologies. These studies have shown that circulating INSL3 is of entirely testicular origin and that the concentrations of this hormone reflect the function of Leydig cells [23]. Also leptin receptors may play a role in reduced androgen levels in obese men as they are present in the testicular tissue; Ishikawa et al. [24], Mah and Wittert [25], and Isidori et al. [26] stated that serum leptin negatively correlated with total and free testosterone, and that leptin was the best hormonal marker low androgen levels in obese men. Later it was demonstrated that leptin receptors were found primarily in Leydig cells as the leptin receptor expression on Leydig cells was inversely correlated with serum testosterone concentration [27]. Excess serum leptin contributes in reducing testosterone levels in obese men [28].

Obese adolescents had insignificant higher ($P>0.05$) mean values of FSH and LH levels than nonobese adolescent men. This higher levels can be due to the low levels of free testosterone and estradiol, which lead to reduced inhibition of gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, which in turn increases the release of LH and FSH, as our patients number may be not be large enough to make significant difference on FSH and LH levels.

When the correlation between anthropometric measurements and hormonal levels of free testosterone estradiol, FSH, and LH was assessed in obese and nonobese adolescents, it was established that there was a significant inverse correlation between free testosterone levels and waist circumference, among obese adolescents. There was also a significant inverse correlation between free testosterone levels and waist circumference in nonobese adolescents a significant inverse correlation between free testosterone level and BMI in obese adolescent men. These results of our study are similar to that done by Mogri et al. [29] in New York which was a cross-sectional observational study done on 25 obese individuals, which demonstrated that the mean free testosterone concentration in obese men was 50% lower than lean men. The mean free testosterone concentration was lower by 46%, while the mean calculated free testosterone concentration was lower by 42% as compared with lean men and the calculated free testosterone concentrations were inversely related to BMI.

Together with our study, Mogri et al. [29] also found that none of the obese patients had significant higher LH or FSH concentrations in comparison with lean cases; this could be due to central suppression of the hypothalamo-hypophyseal-gonadal axis [21] found in obese adolescent men as obesity is an insulin-resistant state with an interference with insulin signal transduction and since insulin is known to facilitate.
GnRH secretion by hypothalamic neurons, *in vitro*, it is possible that this syndrome is a manifestation of insulin resistance at the neuronal level which results in subnormal secretion of GnRH from the hypothalamus [19]. Leptin resistance in obesity may also contribute to hypogonadotropic hypogonadism [20].

Another cross-sectional study done in 2014 by Vandewalle *et al.* [30] on 90 obese adolescent boys and 90 age-matched healthy normal weight controls were randomly selected, they found that in the obese group only waist circumference was inversely correlated with total testosterone (*P*<0.01) and free testosterone (*P*<0.05) levels; however, no associations were found between waist circumference and estradiol.

No significant difference in circulating LH, FSH, and estradiol concentrations was found between obese boys and their controls in both our studies and that of Taneli and colleagues, the secretion of the INSL3 levels in obese adolescent boys, but in the study done by Taneli and colleagues, the secretion of the sertoli cell hormone and inhibin B increases significantly at the onset of puberty (stage 5), so it was found that there were nonsignificant differences in testicular volume in obese and nonobese cases.

When the answers of the MINI-KID module A (presence or absence of depressive symptoms) were compared with the mean free testosterone level among obese and nonobese adolescents, it was established that the mean free testosterone levels was significantly lower in obese than in nonobese adolescents having the following depressive symptoms: feeling depressed, eating disorders (increasing or decreasing appetite), sleeping disorders, feeling restless, feeling guilty, and suicidality; these results may be attributed to the inhibitory effects of testosterone on the hypothalamic-pituitary-adrenal axis [31–32] and it was found that physiological doses of testosterone produce antidepressant-like effects in hypogonadal men [33–34].

When the correlations between depressive symptoms (according to the MINI-KID module A) and hormonal levels of free testosterone, estradiol, FSH, and LH were assessed in obese adolescents, it was established that there were significant inverse correlations between free testosterone level and the following depressive symptoms: feeling depressed, eating disorders, sleeping disorders, feeling restless, feeling guilty, poor concentration, and suicidality, while there were no significant correlations between mean free testosterone level and the following depressive symptoms: feeling tired and loss of interest. Also when the correlations between mild, moderate depression according to CDI (children’s depression inventory) and hormonal levels of free testosterone, estradiol, FSH, and LH were assessed in obese adolescents it was established that there were inverse significant correlations between them as regards the free testosterone level.

In a study done in the USA by Merikangas *et al.* [35], it was found that boys who mature earlier and boys who mature more rapidly than average experience less negative (i.e. less rapid) decreases in depressive symptoms (according to the GDI). Depressive symptoms, on average, decreased during preadolescence. So, boys who matured more quickly than peers reported more depressive symptoms.

Also, there were inverse significant correlations between mild, moderate depression (according to GDI), and hormonal levels of free testosterone in obese adolescents men and there were significant inverse correlations between free testosterone level and the following depressive symptoms (according to the MINI-KID module A): feeling depressed, eating disorders, sleeping disorders, feeling restless, feeling guilty, poor concentration, and suicidality, while there were nonsignificant correlations between mean free testosterone level and depressive symptoms such as loss of interest and feeling tired.

On the other hand, in a study done by Susman *et al.* [36] in the Pennsylvania State, the participants were 56 boys with ages between 10 and 15 years and 52 girls with ages between 9 and 14 year and their parents. The adolescents were recruited into the study until there was approximately an equal number of boys and girls in each of the five stages of pubertal development. There were no relations between depression degree and hormones (total testosterone, estradiol, FSH, and LH) and higher depression symptom scores were related to higher genital stage (testicular volume, axillary, and pubic
conflicts of interest

Nil.

financial support and sponsorship

Nil.

conflicts of interest

There are no conflicts of interest.

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