Evaluation of testicular hormones in obese adolescent males

May Ali Sayed
Prof. Mona Mandyosha Hassan, Professor of Pediatrics Cairo University
Prof. Ahmed Elsharky, Professor of Physiotherapy Institute of Postgraduate Childhood Studies Medical Studies Department
Prof. Azza Sayy Eldein, Professor of Biological Anthropology, National Research Center
Prof. Hanan Hamdy Ahmed, Head of hormones department National Research Center
Dr. Khaled Helmy, Doctor of Biological Anthropology National Research Center

Abstract

**Background:** Previous studies have suggested an association between obesity and testicular function. Aim to investigate the effect of obesity on testicular function by evaluating the reproductive hormones inhibin B and INSL3.

**Subjects and Methods:** This study was a case control study carried out in the "Obesity Clinic of the Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU)" Pediatric Hospital, Cairo University. It included sixty adolescent males complaining of obesity (BMI > 95 percentile) along with twenty normal subjects (BMI = 15. < 85 percentile) matched for age and sex as a control group. Their age was ranged from 12 to 18 years with Tanner stage from 2 to 4. Anthropometric assessment; weight and height; were recorded, and BMI was calculated. Laboratory investigations: inhibin B and INSL3 were measured.

**Results:** Obese boys had significant higher values in BMI and Insulin growth factor 3 (p= 0.001), and significant lower value of Inhibin B than the control normal group. BMI had significant positive correlations with INSL3 (p= 0.000) and significant negative correlation with inhibin B (p= 0.000).

**Conclusion:** Obesity is associated with increased INSL3 (marker of Leydig cell function) and decreased inhibin B (marker of testicular Sertoli cell). Moreover, inhibin B had significant negative correlation with INSL3.

**Key words:** inhibin B, INSL3, adolescent boys, obesity.

(Translation)

**العنوان:** تقييم مستويات الإستروجين (B) والأستروين ميل عامل 3 (INSL3) لدى الأطفال الذين يعانون من السمنة في مرحلة البلوغ.

**الهدف:** إعادة دراسة حالات المجموعة السابقة في زيادة الوزن المتكررة والحمض الدهني وحيدة طبق الأصل مست🎓西班牙 необходимо تمتلئ مكتبة الأطفال في جامعتي القاهرة. وتتم قياس معدل القدرة على الوزن المتكرر وعمر الاداء في العمرية. تم تحليل فصلات تحتوي على بالأولد ممكنية الفرز والذئاب كالأولد ممكنية الفرز.

**المستودعات:** في الدراسة يتم قياس نسبة الإستروجين (B) وآليتي الأستروين ميل عامل 3 (INSL3). انخفضت نسبة الإستروجين (B) وأيضاً ظهرت الدراسة أن الأطفال الذين لديهم أعلى قيم في نسبة الإستروين ميل عامل 3 (INSL3) وأيضاً الذين لديهم أعلى نسبة الإستروجين (B).

**التفسير:** تؤثر السمنة على زيادة الانزيمات في موقع زيادة أفيين آليتي الأستروين ميل عامل 3 (INSL3) وقد قرب الأفيين آليتي الأستروين ميل عامل 3 (INSL3) الأفيين آليتي الأستروين ميل عامل 3 (INSL3).
Introduction:

Obesity defined; by the World Health Organization (WHO); as abnormal or excessive fat accumulation that may impair health. WHO estimates that more than 1.5 billion adults over the age of twenty are overweight and that 1 in 10 adults in the world are obese. It has been suggested that this rising trend of excessive adipose tissue accumulation has not only been caused by an increase in high-sugar and cholesterol-saturated diets, but also by an increase in sedentary lifestyles (Khullar et al., 2012). While obesity has been associated with a host of cardiovascular disease, the metabolic syndrome, and a wide variety of endocrine abnormalities, recent research has suggested a potential link between obesity and testicular affection (Pasquali, 2006; Kasturi et al., 2008; Ferris and Crowther, 2011).

During the first month of life, a phenomenon called "mini-puberty" takes place. It consists of an activation of the hypothalamic-pituitary-testicular axis and it is followed by a period of relative quiescence with low serum levels of gonadotropins and sexual steroids until puberty ensues (Rosita et al., 2014).

In males, Leydig cells produce testosterone and insulin like factor 3 (INSL-3) under stimulation of LH (Ferlin et al., 2006); both testosterone and INSL-3 cause testicular descent before birth. INSL-3 serum concentrations are strongly influenced by the degree of Leydig cells differentiation, in turn, influenced by LH levels (Sadeghiyan et al., 2005; Bay et al., 2006). Mutations of the INSL-3 receptor (Relaxin Family Peptide 2, RXFP2) gene are associated with osteoporosis even in presence of normal serum testosterone concentrations (Ferlin et al., 2008). In addition, INSL-3 increases significantly in a dose dependent manner cAMP in human osteoblasts and stimulate the proliferation of these cells (Ferlin et al., 2009). Sertoli cells produce inhibin B which first increases during the mini-puberty in response to FSH and subsequently during puberty (Rosita et al., 2014). In adult life, the inhibin B serum levels reflect spermatogenesis and exert a negative feedback on FSH secretion (Jorgensen et al., 2010).

The worldwide pandemic of childhood obesity has renewed interest in the relationship between body composition in childhood and the timing and tempo of puberty. Limited evidence suggests that earlier puberty is associated with a tendency towards central fat deposition, in the other direction, rapid early weight gain is associated with advanced puberty in both sexes, and a clear association exists between increasing BMI and earlier pubertal development in girls. Evidence in boys is less clear, with the majority of studies showing obesity to be associated with earlier puberty and voice break, although a subgroup of boys with obesity exhibits late puberty (Wagner et al., 2012).

Aim of the Study:

The present study aims to investigate the effect of obesity on testicular function by evaluating the reproductive hormones inhibin B and insulin-like 3 (INSL3).

Subjects And Methods:

This study was a case control study carried out in the "Obesity Clinic of the Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU)", Pediatric Hospital, Cairo University. It included sixty adolescent males complaining of obesity (BMI ≥ 95 percentile) along with twenty normal subjects (BMI ≤ 150% 85 percentile) matched for age and sex as a control group. Their age was ranged from 12 to 18 years with Tanner stage from 2 to 4. Obese males were having exogenous obesity. We excluded males with any active medical illness, chronic illness as chronic renal failure, celiac disease, ... with history of gonadal dysfunction, under any regular medication and with obesity due to endocrinologic or syndromic cause.

Ethical approval from the "Ethical committee of the National Research Centre" was taken. Informed consent was obtained from the child and the parents after explanation of the aim of the study and its possible benefits for identifying the effect of obesity on health.

Methods:

For each boy participated in the study, detailed history, clinical examination, anthropometric and hormonal assessment were done.

1. History:
   a. Birth Weight.
   b. Onset and duration of obesity.
   c. History of early or delayed puberty in the mother or father or any of his siblings.
   d. Family history of any chronic disease as diabetes mellitus especially in the mother.
   e. History of Playing Sports.
   f. History for the risk factors, morbidities and co-morbidities of obesity.
   g. Symptoms suggestive of secondary diabetes mellitus like polyuria, polydipsia and loss of weight of the child.
   h. Symptoms suggestive of hypertension like headache, epistaxis.

2. Clinical Examination:
   a. Complete clinical examination to exclude any chronic disease.
   b. Measurement of blood pressure.
   c. Pubertal stage assignment and testicular volume estimation were performed using a Prader orchidometer and measuring stretched penile length. The pubertal stage was determined according to Marshall and Tanner 1970.

3. Anthropometric Measurements: Specific anthropometric measurements (Weight, Height and BMI), were calculated using standardized equipments, and following the recommendations of the International Biological Program by (Weiner and Lourie, 1969).

4. Laboratory Investigations:
   a. Venous blood samples were obtained between 8:00 and 10:00 hours after 10 h of fasting. After clotting the blood samples were centrifuged and the sera were separated and kept at -80 °C for batch assessments.
   b. Serum Inhibin B and INSL3 were measured by electro-
Results:
The study included 60 obese pubertal boys and 20 normal (control) pubertal boys whose age ranged between 12 and 18 years. Comparison between the two groups regarding BMI and laboratory findings was presented in Table 1.

Obese boys had significantly higher values in BMI and insulin growth factor-3 (p = 0.001), and significantly lower value of Inhibin B than the control normal group.

Table (1) Comparison between obese and normal boys as regard BMI, Inhibin B and INSL3.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>N</th>
<th>Mean ± S.D.</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Normal</td>
<td>20</td>
<td>20.99 ± 10.46</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>60</td>
<td>53.0 ± 13.17</td>
<td></td>
</tr>
<tr>
<td>Inhibin B (ng/L)</td>
<td>Normal</td>
<td>20</td>
<td>85.28 ± 27.66</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>60</td>
<td>62.00 ± 17.85</td>
<td></td>
</tr>
<tr>
<td>Insulin growth factor-3 (ng/L)</td>
<td>Normal</td>
<td>20</td>
<td>3.80 ± 0.72</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>60</td>
<td>3.69 ± 1.04</td>
<td></td>
</tr>
</tbody>
</table>

Table (2) shows correlations between BMI, age, inhibin B and INSL3.

BMI had significant positive correlations with INSL3 (p = 0.000) and significant negative correlation with inhibin B (p = 0.004). Moreover, inhibin B had significant negative correlation with INSL3 (P = 0.027). Age had insignificant correlations with either INSL3 (p = 0.162) or inhibin B (p = 0.973).

Table (3) Correlation between BMI, INSL3 and Inhibin B.

<table>
<thead>
<tr>
<th>BMI Z</th>
<th>Inhibin B</th>
<th>INSL3</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>0.162</td>
<td>0.362</td>
</tr>
<tr>
<td>Inhibin B (ng/L)</td>
<td>-0.33</td>
<td>0.004</td>
</tr>
<tr>
<td>INSL3 (ng/L)</td>
<td>0.63</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Discussion:
In the present study, serum INSL3 level significantly increased about 2 folds in obese boys than normal weight ones. BMI also had significant positive correlations with INSL3 (p = 0.000) Previous studies stated that serum INSL3 concentrations in adolescent boys showed a significant rise during pubertal stages and positively correlated with testicular growth (Ferrin et al., 2006; Feng et al., 2009; Wikström et al., 2006). Continuous increase in INSL3 levels during puberty is evidence that INSL3 may be used as a Leydig cell specific marker for onset and succession of puberty in boys (Bay et al., 2007). We believe that obesity lead to significant more increase in INSL3, the marker of Leydig cell function, than among pubertal normal weight boys. So, INS/3 or Leydig cells are affected by obesity in the pubertal period but there are no other literatures support our finding.

In contrary, in the present study, we found that obese boys had significantly lower value of serum inhibin B (p = 0.001) than non-obese boys. BMI had significant negative correlation with inhibin B (p = 0.004). Moreover, inhibin B had significant negative correlation with INSL3 (P = 0.027).

In agreement with current results, Radionchii et al., (2005) reported that inhibin B levels increase regularly during puberty until they reach adult levels in late puberty. They believed that inhibin B is increased in association with the progressive increase in testis volume and spermatogenesis occurring in late puberty. Aggerholm et al. (2008) found that serum inhibin B concentrations were (25%-32%) lower in obese men in comparison with normal weight men. Winters et al. (2006) demonstrated that inhibin B levels declined with increasing obesity in young adult men while it was normal in prepubertal boys (Fu et al., 2006). In the present study, we believed that inhibin B, the marker of Sertoli cell function is sensitive and Sertoli cells are affected by obesity in the pubertal period.

Current study revealed that age had insignificant correlations with either INSL3 (p = 0.162) or inhibin B (p = 0.973). This confirms that age had no effect on the relations between these hormones and obesity or between each other.

Conclusions:
This study demonstrated that obesity is associated with increase INSL3 (marker of Leydig cell function) and decrease inhibin B (marker of testicular Sertoli cell). Moreover, inhibin B had significant negative correlation with INSL3.

References:


